DESCRIPTION

SUBSTITUTED KETOPHOSPHONATE COMPOUNDS HAVING BONE ANABOLIC ACTIVITY

FIELD OF INVENTION

The present invention relates to the use of novel substituted ketophosphonate compounds in the treatment and/or prevention of bone diseases requiring, such as osteoporosis, through enhanced bone anabolic activity.

BACKGROUND OF THE INVENTION

Bone remodelling and repair is a tightly regulated process that continues throughout a person's lifetime. Bone formation requires the activity of the osteoblasts, the bone forming cells, whereas bone resorption results from the action of the osteoclasts. Consequently, two therapeutic approaches toward bone mass manipulation are currently investigated, namely, prevention of bone resorption and stimulation of bone formation (bone anabolism).

A preferred approach for the prevention and/or treatment of bone diseases is to increase bone formation by stimulation of osteoblasts. However, the large majority of therapeutic agents which stimulate bone formation or inhibit bone turnover are hormones or derivatives of hormones (estrogens, anabolic steroids, calcitonin, parathyroid hormone, vitamin D) with numerous side effects resulting from their hormonal activities. Sodium fluoride, the old prophylatic for dental caries, is still the most widely used compound for the stimulation of bone formation. There is thus a need for new active compounds, preferably oral agents, that act by stimulating bone formation.

The bisphosphonic acids (BP; also known as diphosphonic acids) and their salts are a class of compounds that are cytotoxic to osteoclasts and act to prevent bone resorption. These compounds have no effect on osteoblasts. Anti-resorptive bisphosphonic acids are currently used for the treatment of various bone diseases such as osteoporosis, hypercalcemia due to malignancies and inhibition of tumor cell metastasis in bone tissue. Despite their proven pharmacologic efficacy, the clinical utility of bisphosphonic acids is limited by their very low oral bioavailability and their gastrointestinal toxicity.

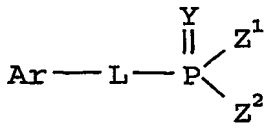
It has also been reported that statins have bone anabolic activity and prevent fractures in patients. These compounds, known to be HMG-CoA reductase inhibitors, were found to increase the synthesis of bone morphogenic protein 2 (BMP-2), a growth factor that triggers osteoblast differentiation to form new bone (see Mundy *et al.*, 1999). The mechanism of the effect of statins on bone anabolism remains to be elucidated.

Although the fact that HMG-CoA reductase inhibitors induce BMP-2 synthesis and osteoblastic differentiation is well established, there remains a need to identify compounds with bone anabolic activity that are not solely competitive inhibitors of HMG-CoA reductase, as this class of inhibitors is characterized by a high degree of toxicity when systemically available. Furthermore, current inhibitors of HMG-CoA reductase were designed to target the liver and induce hypocholesterolemia, and are also known to trigger a positive feed-back resulting in the upregulation of the large majority of genes involved in isoprenoids and cholesterol synthesis. Thus, these compounds have significant drawbacks in the context of the treatment of bone diseases.

Consequently, it would be useful to identify synthetic compounds which decrease HMG-CoA reductase levels leading to bone anabolic activity.

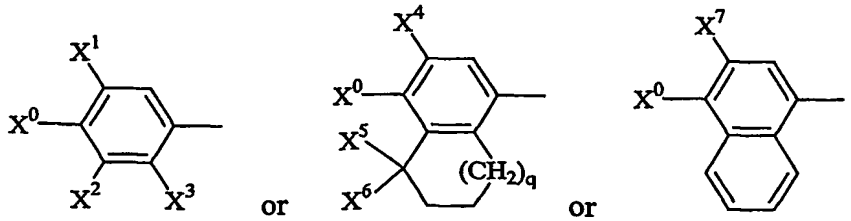
SUMMARY OF THE INVENTION

The Applicants have now found that substituted phosphonates of formula (I), as set out below, have bone anabolic activity and are thereby useful in the treatment of bone diseases. One aspect of the invention are substituted phosphonate compounds of the formula (I):



(I)

wherein Ar is:



and X^0 is H, OH or a straight or branched C_1 to C_6 alkoxy group,

X^1, X^2 and X^3 are independently H, OH, a straight, branched or cyclic C_1-C_6 alkyl or alkoxy group;

or X^0, X^1 or X^2, X^3 together may form a C_1 - C_8 optionally substituted alkylidenoxy or alkylidenedioxy group;

with the proviso that X^0 is H when X^3 is H and X^1 and X^2 are independently straight or branched C_1 - C_6 alkyl groups;

X^4, X^5, X^6 are independently H, a straight or branched $C_1 - C_6$ alkyl group;

q is zero or 1;

X^7 is H, a straight or branched $C_1 - C_8$ alkyl or alkoxy group, or an optionally substituted benzyl group;

Y is O or S;

Z^1 and Z^2 are independently OR^1 or NR^2R^3, where R^1, R^2, and R^3 are independently H or a straight or branched C_1 - C_6 alkyl group, or Z^1, Z^2 together may form a C_2 - C_8 alkylidenedioxy group; and

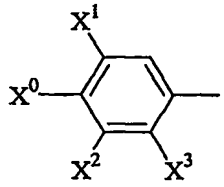
L is a saturated or unsaturated C_1 - C_{11} alkylene chain in which one or more of the methylene groups can be replaced by a sulfur atom, an oxygen atom, a carbonyl group wherein optionally one or more methylene groups can be substituted by one or more halogen atoms (F, Cl or Br), C_1-C_6 alkyl, an optionally substituted aryl or heteroaryl group. The present invention also encompasses pharmaceutically acceptable salts, solvates and hydrates of compounds of formula (I).

In various embodiments of the present invention, L is -A-C(O)-B-, wherein "-A-" is a direct bond, $-CH=C(R^4)-$,$-CH_2-C(R^4)(R^5)-$, $-C(R^4)(R^5)-$, $-O-C(R^4)(R^5)-$, $-S-C(R^4)(R^5)-$, where R^4,R^5 are independently or different are, H, halogen (F, Cl, Br), C_1-C_6 straight or branched alkyl, an optionally substituted aryl or heteroaryl,

"-B-" is $-C(R^6)(R^7)-$ where R^6,R^7 identical or different are H, Halogen (F, Cl, Br), C_1-C_6 straight or branched alkyl, an optionally substituted aryl or heteroaryl, or R^6 and R^7 can form a ring of C_3-C_7 carbon atoms.

The term "alkyl" and "alkoxy" as used herein in relation to X^0, X^1, X^2, X^3, X^6, R^1, R^2, R^3, R^4 and R^5 means as indicated saturated straight, branched or cyclic substitutents, *i.e.*, straight or branched $-(C_nH_{2n+1})$ or $-O(C_nH_{2n+1})$ or cyclic $-(C_nH_{2n-1})-$ or $-O-(C_nH_{2n-1})-$, and also includes halogenated alkyl and alkoxy groups and derivatives thereof, such as fluoro-substituted groups, fluorohydroxy substituted groups wherein the degree of halogenation ranges from a single halo substituent, *e.g.*, $-CH_2F$ and $-OCH_2F$, to perhalo-substituted alkyl and alkoxy groups, *e.g.*, $-CF_3$ and $-OCF_3$.

In some embodiments, Ar is:



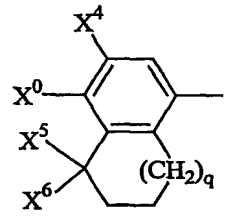
wherein X^0 is H, OH, OMe, X^3 is H, OH, Me, OMe, X^1 and X^2 are independently a straight or branched $C_1 - C_6$ alkyl, a straight or branched $C_1 - C_6$ alkoxy group;

with the proviso that X^0 is H when X^3 is H, and X^1 and X^2 are independently a straight or branched $C_1 - C_6$ alkyl groups;

Y is O; Z^1 and Z^2 are the same and are OR^1 wherein R^1 is methyl, ethyl or isopropyl;

L is $CH=C(R^4)-CO-C(R^6R^7)$, or $-COC(R^6)(R^7)$-wherein R^4, R^6 and R^7 are as previously defined, and in some embodiments L is $CH=CH-CO-C(CH_3)_2$, $CH=CH-CO-CH_2$, $CH=CH-CO-C(CH_3)(F)$, $CH=CH-CO-C(F)_2$, or $CO-CH_2$, $CO-C(CH_3)_2$, $CO-C(CH_3)(F)$, $CO-C(F)_2$.

In another embodiment, Ar is:



wherein X^0 is H, OH, OMe;

X^4 is H, a straight, branched or cyclic C_1 to C_8 alkyl or alkoxy group, more preferably X^4 is a tert-butyl group;

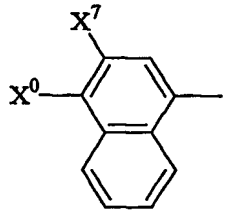
X^5 and X^6 are indepdently H, a C_1-C_4 alkyl group, more preferably X^5 and X^6 are H;

q is zero or 1, more preferably q is 1;

Y is O; Z^1 and Z^2 are the same and are OR^1 wherein R^1 is methyl, ethyl or isopropyl;

L is $CH=C(R^4)-CO-C(R^6R^7)$, or $-COC(R^6)(R^7)$-wherein R^4, R^6 and R^7 are as previously defined, and in some embodiments L is $CH=CH-CO-C(CH_3)_2$, $CH=CH-CO-CH_2$, $CH=CH-CO-C(CH_3)(F)$, $CH=CH-CO-C(F)_2$, or $CO-CH_2$, $CO-C(CH_3)_2$, $CO-C(CH_3)(F)$, $CO-C(F)_2$.

In a further embodiments Ar is:



wherein X^0 is H, OH, SH, OMe, SMe group;

X^7 is H, a straight or branched $C_1 - C_8$ alkyl or alkoxy group, preferably a t-butyl group or an optionally substituted benzyl group;

Y is O;

Z^1 and Z^2 are the same and are OR^1 wherein R^1 is methyl, ethyl or isopropyl;

L is $CH=C(R^4)-CO-C(R^6R^7)$, or $-COC(R^6)(R^7)$-wherein R^4, R^6 and R^7 are as previously defined, and in some embodiments L is $CH=CH-CO-C(CH_3)_2$,$CH=CH-CO-CH_2$, $CH=CH-CO-C(CH_3)(F)$, $CH=CH-CO-C(F)_2$, or $CO-CH_2$, $CO-C(CH_3)_2$, $CO-C(CH_3)(F)$, $CO-C(F)$.

In various further embodiments, the novel substituted phosphonate compound of formula (I) is selected from the group consisting of:

dimethyl 4-(3-methoxy-5-methyl-4-hydroxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;

dimethyl 4-(3,5-dimethoxy-4-hydroxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;

dimethyl 4-(3,4,5-trimethoxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;

dimethyl 4-(4,5-dimethoxy-3-hydroxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;

dimethyl 4-(3,5-diethoxy-4-hydroxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;

dimethyl 4-(4-hydroxy-3-methoxy-5-n-propylphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;

dimethyl 4-(5-tert-butyl-2-hydroxy-3-methoxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;

dimethyl 4-(3-cyclopentyloxy-4-methoxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;

dimethyl 4-(3,5-di-cyclopentyl-4-hydroxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;

diethyl 2-(3,4,5-trimethoxyphenyl)-1,1-dimethyl-2-oxo-ethylphosphonate;

dimethyl 4-(3,5-di-tert-butyl-2-hydroxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl phosphonate;

diethyl 4-(3,5-di-tert-butyl-2-hydroxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl phosphonate;

dimethyl 4-(3,5-di-tert-butyl-2-hydroxyphenyl)-1,1-diethyl-2-oxo-3-buten-1-yl phosphonate;

diethyl 4-(3,5-di-tert-butyl-2-hydroxyphenyl)-1,1-diethyl-2-oxo-3-buten-1-yl phosphonate;
dimethyl 4-(3,5-di-tert-butyl-2-hydroxyphenyl)-1,1-cyclopentyliden-2-oxo-3-buten-1-yl phosphonate;
diethyl 4-(3,5-di-tert-butyl-2-hydroxyphenyl)-1,1-cyclopentyliden-2-oxo-3-buten-1-yl phosphonate;
diethyl 4-(3,5-di-tert-butyl-2-hydroxyphenyl)-1-fluoro-1-methyl-2-oxo-3-buten-1-yl phosphonate;
dimethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-2-oxo-3-buten-1-yl phosphonate;
diethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-2-oxo-3-buten-1-yl phosphonate;
dimethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl phosphonate;
diethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl phosphonate;
diisopropyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl phosphonate;
dimethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1-methyl-2-oxo-3-buten-1-yl phosphonate;
diethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1-methyl-2-oxo-3-buten-1-yl phosphonate;
dimethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1-fluoro-1-methyl-2-oxo-3-buten-1-yl phosphonate;
diethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1-fluoro-1-methyl-2-oxo-3-buten-1-yl phosphonate;
dimethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1,1-difluoro-2-oxo-3-buten-1-yl phosphonate;
diethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1,1-difluoro-2-oxo-3-buten-1-yl phosphonate;
dimethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1,1-diethyl-2-oxo-3-buten-1-yl phosphonate;
dimethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1,1-cyclopentyliden-2-oxo-3-buten-1-yl phosphonate;
diethyl 2-(3,5-di-tert-butyl-2-methoxyphenyl)-1-methyl-2-oxoethylphosphonate;
diethyl 2-(3,5-di-tert-butyl-2-methoxyphenyl)-1,1-dimethyl-2-oxoethylphosphonate;
dimethyl 2-(3,5-di-tert-butyl-2-methoxyphenyl)-1-fluoro-1-methyl-2-oxoethylphosphonate;
diethyl 2-(3,5-di-tert-butyl-2-methoxyphenyl)-1-fluoro-1-methyl-2-oxoethylphosphonate;
dimethyl 4-(3,5-di-tert-butylphenyl)-2-oxo-3-buten-1-yl phosphonate;
diethyl 4-(3,5-di-tert-butylphenyl)-2-oxo-3-buten-1-yl phosphonate;
dimethyl 4-(3,5-di-tert-butylphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl phosphonate;
diethyl 4-(3,5-di-tert-butyl-phenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl phosphonate;
dimethyl 4-(3,5-di-tert-butylphenyl)-1-ethyl-1-methyl-2-oxo-3-buten-1-yl phosphonate;
dimethyl 4-(3,5-di-tert-butylphenyl)-1,1-diethyl-2-oxo-3-buten-1-yl phosphonate;

dimethyl 4-(3,5-di-tert-butylphenyl)-1,1-cyclopentyliden-2-oxo-3-buten-1-yl phosphonate;

dimethyl 4-(3,5-di-tert-butylphenyl)-1,1-fluoro-2-oxo-3-buten-1-yl phosphonate;

diethyl 4-(3,5-di-tert-butyl-phenyl)-1,1-fluoro-2-oxo-3-buten-1-yl phosphonate;

dimethyl 2-(3,5-di-tert-butylphenyl)-1-methyl-2-oxoethylphosphonate;

diethyl 2-(3,5-di-tert-butyl-phenyl)-1-methyl-2-oxoethylphosphonate;

dimethyl 2-(3,5-di-tert-butylphenyl)-1,1-dimethyl-2-oxoethylphosphonate;

diethyl 2-(3,5-di-tert-butyl-phenyl)-1,1-dimethyl-2-oxoethylphosphonate;

dimethyl 2-(3,5-di-tert-butylphenyl)-1-fluoro-1-methyl-2-oxoethylphosphonate;

diethyl 2-(3,5-di-tert-butylphenyl)-1-fluoro-1-methyl-2-oxethylphosphonate;

dimethyl 2-(3,5-di-tert-butylphenyl)-1,1-difluoro-2-oxoethylphosphonate;

dimethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-2-oxo-3-buten-1-yl-phosphonate;

diethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-2-oxo-3-buten-1-yl-phosphonate;

dimethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;

diethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;

dimethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-1-methyl-2-oxo-3-buten-1-yl-phosphonate;

diethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-1-methyl-2-oxo-3-buten-1-yl-phosphonate;

dimethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-1-fluoro-1-methyl-2-oxo-3-buten-1-yl-phosphonate;

diethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-1-fluoro-1-methyl-2-oxo-3-buten-1-yl-phosphonate;

dimethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-1-ethyl-1-methyl-2-oxo-3-buten-1-yl-phosphonate;

dimethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-1,1-diethyl-2-oxo-3-buten-1-yl-phosphonate;

dimethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-1,1-cyclopentylidene-2-oxo-3-buten-1-yl-phosphonate;

dimethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-2-oxo-3-buten-1-yl-phosphonate;

diethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl-2-oxo-3-buten-1-yl-phosphonate;

dimethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;

diethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;

diisopropyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;

dimethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1-methyl-2-oxo-3-buten-1-yl-phosphonate;

diethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1-methyl-2-oxo-3-buten-1-yl-phosphonate;

dimethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1-fluoro-1-methyl-2-oxo-3-buten-1-yl-phosphonate;

diethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1-fluoro-1-methyl-2-oxo-3-buten-1-yl-phosphonate;

dimethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1-ethyl-1-methyl-2-oxo-3-buten-1-yl-phosphonate;

dimethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1,1-diethyl-2-oxo-3-buten-1-yl-phosphonate;

dimethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1,1-cyclopentylidene-2-oxo-3-buten-1-yl-phosphonate;

diethyl 2-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1-methyl-2-oxoethyl phosphonate;

diethyl 2-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1-fluoro-1-methyl-2-oxo-ethylphosphonate;

dimethyl 4-(3-tert-butyl-5,5-dimethyl-4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;

dimethyl 4-(3-tert-butyl-4-hydroxy-1-naphthyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;

dimethyl 4-(3-benzyl-4-hydroxy-1-naphthyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;

dimethyl 4-(3,5-di-tert-butyl-2-hydroxyphenyl)-1,1-dimethyl-2-oxo-1-butyl-phosphonate;

dimethyl 4-(5-tert-butyl-2-hydroxy-3-methoxyphenyl)-1,1-dimethyl-2-oxo-1-butyl-phosphonate; and

dimethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-1,1-dimethyl-2-oxo-1-butyl-phosphonate.

Embodiments also encompass pharmaceutical compositions of the substituted phosphonate compounds of formula (I) comprising a pharmaceutically acceptable carrier.

Another aspect of the present invention is a method of treating or preventing a bone disease or pathology, comprising administering to a subject in need of such treatment an amount effective to stimulate bone formation of a substituted phosphonate compound of formula (I).

In some embodiments, the bone disease or pathology is osteoporosis, Paget's disease, bone fracture, hormone-induced bone pathologies, hyperparathyroidism, peridontal disease, post-plastic surgery, post-prosthetic joint surgery, post-dental implantation, hypercalcemia secondary to malignancies or hyperparathyroidism, a condition arising from hypercalcemia, including calcification of soft tissue (*e.g.*, kidney, vessel walls and heart values), calcification of surgical implants and calcification of arteries (*e.g.*, due to late stage atherosclerosis). In some embodiments, the subject is characterized by a condition selected from the group consisting of osteoporosis, Paget's disease, bone fracture or deficiency, drug and hormone-induced bone pathologies (*e.g.*, corticoids, retinoids and vitamin D3 induced bone pathologies), hyperparathyroidism, periodontal disease or defect, post-plastic surgery, post-prosthetic joint surgery post-dental implantation, metastasis of cancer cells in bones, including osteolytic or osteoplastic bone metastasis, tumoral osteolysis, and hypercalcemia, wherein said hypercalcemia is secondary to malignancies.

In some embodiments, the method further comprises administration to the subject an effective amount of a bone resorption inhibitor, which may be alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zoledronate, midronic acid, icandronic acid, S-12911, raloxifene, simvastatin, atorvastatin, cerivastatin, vitamin D or calcitonin.

DETAILED DESCRIPTION OF THE INVENTION

I. Bone Anabolic Substituted Phosphonate Compounds

While the present invention is not bound by any particular theory, it is believed that the compounds of formula (I) modify bone formation by affecting the mevalonate/isoprenoid/cholesterol (MIC) pathway. The administration of statins, competitive inhibitors of HMG-CoA reductase (a rate-limiting step in cholesterol synthesis), results in increased bone morphogenetic protein-2 (BMP-2) levels and thereby stimulates osteoblast differentiation. Apart from cholesterol, the MIC pathway also provides isoprenoids, *e.g.*, farnesylpyrophosphate and geranylgeranylpyrophosphate, compounds that serve as important lipid anchors for the post-translational modification of a variety of cell signalling proteins such as Rap, Ras and Rho. These signalling proteins, when anchored in the osteoclast cell membrane

by a lipid prenyl group, regulate the osteoclast cell processing required for active bone resorption, *e.g.*, cytoskeleton organization and membrane ruffling. The discovery that the compounds of formula (I) decrease the level of HMG-CoA reductase, tends to indicate that these compounds may be useful for the treatment of bone diseases, as verified by their bone anabolic activity in animal models

Pharmaceutically acceptable salts for use in the present invention include those described by Berge *et al.* (1977). Such salts may be formed from inorganic and organic acids. Representative examples thereof include salts formed from alkali metals such as potassium and sodium.

Since the compounds of the present invention are intended for use in pharmaceutical compositions, it will be understood that they are each provided in substantially pure form, for example at least 50% pure, more suitably at least 75% pure and preferably at least 95% pure (% are on a wt/wt basis). Impure preparations of the compounds of formula (I) may be used for preparing the more pure forms used in the pharmaceutical compositions. Although the purity of intermediate compounds of the present invention is less critical, it will be readily understood that the substantially pure form is preferred as for the compounds of formula (I). Preferably, whenever possible, the compounds of the present invention are obtained in crystalline form.

When some of the compounds of this invention are allowed to crystallise or are recrystallised from organic solvents, solvent of crystallisation may be present in the crystalline product. This invention includes within its scope such solvates. Similarly, some of the compounds of this invention may be crystallised or recrystallised from solvents containing water. In such cases water of hydration may be formed. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation. In addition, different crystallisation conditions may lead to the formation of different polymorphic forms of crystalline products. This invention includes within its scope all polymorphic forms of the compounds of formula (I).

II. Formulations and Administration

The compounds of formula (I) can be administered by any of a variety of routes. Thus, for example, they can be administered orally, or by delivery across another mucosal surface (for example across the nasal, buccal, bronchial or rectal mucosa), transdermally, or by injection (for example intradermal, intraperitoneal, intravenous or intramuscular injection).

When the compounds are intended for oral administration, they can be formulated, for example, as tablets, capsules, ovules, granules, pills, lozenges, powders, solutions, emulsions,

syrups, elixirs, suspensions, or any other pharmaceutical form suitable for oral administration. Oral dosage forms can, if desired, be coated with one or more release delaying coatings to allow the release of the active compound to be controlled or targeted at a particular part of the enteric tract.

Tablets and other solid or liquid oral dosage forms can be prepared (*e.g.*, in standard fashion) from the compounds of formula (I) and a pharmaceutically acceptable solubilizer, diluent or carrier. Examples of solubilizers, diluents or carriers include sugars such as lactose, starches, cellulose and its derivatives, powdered tracaganth, malt, gelatin, talc, stearic acid, magnesium stearate, calcium sulfate, vegetable oils, polyols such as glycerol, propyleneglycol and polyethyleneglycols, alginic acids and alginates, agar, pyrogen free water, isotonic saline, phosphate buffered solutions, and optionally other pharmaceutical excipients such as disintegrants, lubricants, wetting agents such as sodium lauryl sulfate, coloring agents, flavoring agents and preservatives, *etc.*

Capsules can be of the hard or soft variety and can contain the active compound in solid, liquid or semisolid form. Typically such capsules are formed from gelatine or an equivalent substance and can be coated or uncoated. If it is desired to delay the release of the active compound until the capsule has passed through the stomach and into the intestine, the capsule can be provided with a pH sensitive coating adapted to dissolve at the pH found in the duodenum or ileum. Examples of such coatings include the Eudragits, the uses of which are well known.

Formulations for injection will usually be made up of the appropriate solubilizers such as detergents which may also include compounds and excipients such as buffering agents to provide an isotonic solution having the correct physiological pH. The injectable solutions are typically pyrogen-free and can be provided in sealed vials or ampoules containing a unit dose of compound. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavoring or coloring agents.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can

be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatine capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

A typical suppository formulation comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins or cocoa butter or other low melting vegetable or synthetic waxes or fats.

Preferably the composition is in unit dose form such as a tablet or capsule.

The choice of form for administration as well as effective dosages will vary depending, inter alia, on the condition being treated. The choice of mode of administration and dosage is within the ability of the person skilled in the art.

A unit dosage form of the compounds of the invention typically will contain from 0.1% to 99% by weight of the active substance, more usually from 5% to 75% of the active substance. By way of example, a unit dosage form can contain from 1 mg to 1 g of the compound, more usually from 10 mg to 500 mg, for example between 50 mg and 400 mg, and typically in doses of 100 mg to 200 mg.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the structure (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The compounds of the invention will be administered in amounts that are effective to provide the desired therapeutic effect. The concentrations necessary to provide the desired therapeutic effect will vary according to among other things the precise nature of the disease, the size, weight and age of the patient and the severity of the disease.

The doses administered will preferably be non-toxic to the patient, although in certain circumstances the severity of the disease under treatment may necessitate administering an amount of compound that causes some signs of toxicity.

Typically, the compounds of the invention will be administered in amounts in the range 0.01 mg/kg to100 mg/kg body weight, more preferably 0.1 mg/kg to 10 mg/kg body weight and particularly 1 mg/kg to 5 mg/kg body weight.

The pharmaceutically acceptable compounds of the invention will normally be administered to a subject in a daily dosage regimen. For an adult patient this may be, for example, an oral dose of between 1 mg and 500 mg, preferably between 1 mg and 250 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 25 mg, of the compound of the structure (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Thus, for an average human of 70 kg weight, a typical daily dosage of the compounds of the invention would be in the range of 70 mg to 700 mg. Such a dosage can be administered, for example from two to four times daily.

Ultimately however, the size of the doses administered and the frequency of administration will be at the discretion and judgement of the physician treating the patient.

The compounds of the invention may also be administered in combination with an effective amount of a bone resorption inhibitor. Bone resorption inhibitors are those agents known in the art to inhibit the absorption of bone and include, but are not limited to the following classes of compounds: bisphosphonic acids, such as alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zoledronate, midronic acid, icandronic acid, and S-12911; Selective Estrogen Receptor Modulators (SERMs), such as: raloxifene; HMG-CoA reductase inhibitors, such as simvastatin, atorvastatin and cerivastatin; steroid hormones, such as Vitamin D; and polypeptide hormones, such as calcitonin. Dosage ranges and regimens for bone resorption inhibitors are those which are known in the art. In particular, when a bisphosphonic acid is employed, a daily dosage of 2.5 to 100 mg may be used. In accordance with the method of the present invention, the components of a combination of the compounds of the present invention and bone resorption inhibitors can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. According to the instant invention, the term "administering" is to be understood as embracing all such regimes of simultaneous or alternating treatment and the scope of combinations of the compounds of this invention and bone resorption inhibitors includes in principle, any combination useful for inhibiting bone loss and building new bone.

Disease states which could benefit from increasing bone formation include, but are not limited to: osteoporosis; prevention and accelerated repair of bone fracture; prevention and treatment of metastasis of cancer cells in bone; prevention and treatment of osteolytic bone lesions; prevention and treatment of osteoblastic bone metastasis; prevention and treatment of increased bone remodeling, bone hypertrophy and abnormal bone structure (*i.e.*, Paget's

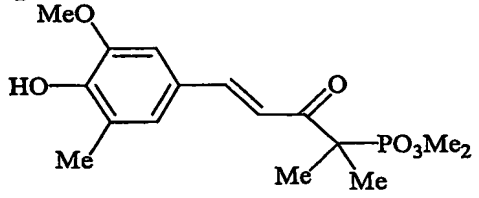
disease); prevention and treatment of bone loss associated with cancer therapies (*e.g.*, bone loss associated with the treatment of gonadotropin-releasing hormone agonists for prostate cancer and bone loss associated with chemotherapy for breast cancer, wherein such chemotherapy includes, but is not limited to, cyclophosphamide, methotrexate, fluorouracil, paclitaxel, doxorubicin, tamoxifen and combinations thereof); prevention and treatment of bone loss in HIV patients associated with lipodsytrophy and treatment with antiviral drugs; prevention of the calcification of soft tissues (*i.e.*, kidneys and other organs); prevention of the calcification of surgical implants (*i.e.*, natural and artificial organs such as cardiac valves); treatment of patients suffering from calcified soft tissues and calcified surgical implants; prevention and treatment of calcification and calcified arteries (arteriosclerosis); hypercalcemia secondary to an increase in bone resorption; hypercalcemia secondary to malignancies; tumoral osteolysis; drug and hormonal (*e.g.*, corticoids, retinoid, vitamin D3) induced bone pathologies; bone remodelling (plastic surgery); operative repair of cartilage; dental surgery; and orthodontic pathologies.

The compounds of this invention increase bone formation and are therefore of value in the treatment of any of these conditions.

EXAMPLES OF THE INVENTION

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following specific examples are intended merely to illustrate the invention and not to limit the scope of the disclosure or the scope of the claims in any way whatsoever.

Example 1: Dimethyl 4-(3-methoxy-5-methyl-4-hydroxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate



The procedure described in the Example 22 was followed, using 4-hydroxy-3-methoxy-5-methylbenzaldehyde (1.16 g, 6.6 mmol). The crude compound obtained was purified by flash column chromatography (SiO_2, 98/2 AcOEt/MeOH). An amount of 0.93 g (2.7 mmol, 41 % yield) of the title compound was obtained.

MS: m/e = 342: M^+, 232: M^+ - HPO_3Me_2, 191 (100%): M^+- $CMe_2(PO_3Me_2)$

NMR: ($CDCl_3$)

δ = 7.62 (d, J = 16Hz, 1H): Ph-C<u>H</u>=CH

7.27 (d, J = 16Hz, 1H): Ph-CH=C<u>H</u>

7.06 and 6.95 (two m, total 2H): arom. H

6.0 (s, 1H): OH

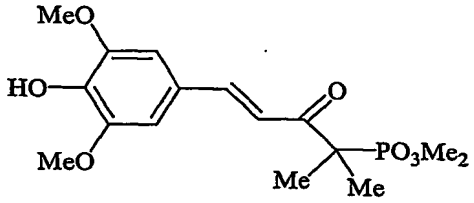
3.93 (s, 3H): arom. O-C<u>H</u>$_3$

3.79 (d, J = 11 Hz, 6H): P-O-C<u>H</u>$_3$

2.27 (s, 3H): arom. C<u>H</u>$_3$

1.51 (d, J = 16.5Hz, 6H): -C(C<u>H</u>$_3$)$_2$-P

Example 2: Dimethyl 4-(3,5-dimethoxy-4-hydroxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate



The procedure described in the preceding example was followed, using 3,5-di-methoxy-4-hydroxybenzaldehyde (1.2 g, 6.6 mmol). The crude compound obtained was purified by flash column chromatography (SiO_2, 98/2 AcOEt/MeOH). An amount of 0.56 g (1.6 mmol, 26 % yield) of the title compound was obtained.

MS: m/e = 358: M^+, 248: M^+ - HPO_3Me_2, 207 (100%): M^+- $CMe_2(PO_3Me_2)$

NMR: ($CDCl_3$)

δ = 7.62 (d, J = 15.5Hz, 1H): Ph-C<u>H</u>=CH

7.28 (d, J = 16Hz, 1H): Ph-CH=C<u>H</u>

6.85 (s, 2H): arom. H

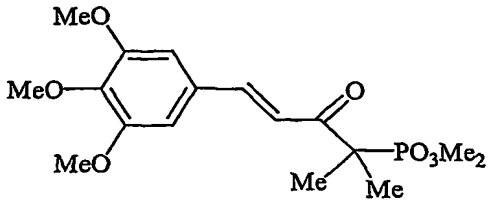
5.9 (s, 1H): OH

3.94 (s, 6H): arom. O-C<u>H</u>$_3$

3.79 (d, J = 11 Hz, 6H): P-O-C<u>H</u>$_3$

1.52 (d, J = 16.5Hz, 6H): -C(C<u>H</u>$_3$)$_2$-P

Example 3: Dimethyl 4-(3,4,5-trimethoxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate



The procedure described in the preceding example was followed, using 3,4,5-trimethoxybenzaldehyde (1.3 g, 6.6 mmol). The crude compound obtained was purified by flash column chromatography (SiO_2, 98/2 AcOEt/MeOH). An amount of 1.12 g (3.1 mmol, 45 % yield) of the title compound was obtained.

MS: m/e = 372: M^+, 262: M^+ - HPO_3Me_2, 221 (100%): M^+- $CMe_2(PO_3Me_2)$

NMR: ($CDCl_3$)

δ = 7.61 (d, J = 15.5Hz, 1H): Ph-C<u>H</u>=CH

7.32 (d, J = 15.5Hz, 1H): Ph-CH=C<u>H</u>

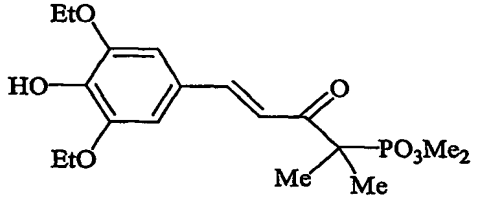
6.83 (s, 2H): arom. H

3.91 and 3.89 (two s, total 9H): arom. O-C<u>H</u>$_3$

3.79 (d, J = 11 Hz, 6H): P-O-C<u>H</u>$_3$

1.52 (d, J = 16.5Hz, 6H): -C(C<u>H</u>$_3$)$_2$-P

Example 4: Dimethyl 4-(3,5-diethoxy-4-hydroxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate



The procedure described in the preceding example was followed, using 3,5-di-ethoxy-4-hydroxybenzaldehyde (1.4 g, 6.6 mmol). The crude compound obtained was purified by flash column chromatography (SiO_2, 98/2 AcOEt/MeOH). An amount of 1.6 g (4.1 mmol, 62 % yield) of the title compound was obtained.

MS: m/e = 386: M^+, 276: M^+ - HPO_3Me_2, 235 (100%): M^+- $CMe_2(PO_3Me_2)$

NMR: ($CDCl_3$)

δ = 7.59 (d, J = 16Hz, 1H): Ph-C<u>H</u>=CH

7.26 (d, J = 16Hz, 1H): Ph-CH=C<u>H</u>

6.84 (s, 2H): arom. H

5.84 (s, 1H): OH

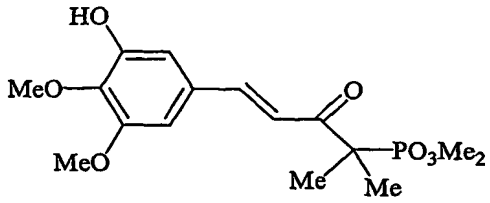
4.17 (q, J = 7Hz, 4H): arom. O-C<u>H</u>$_2$-CH$_3$

3.78 (d, J = 11 Hz, 6H): P-O-C<u>H</u>$_3$

1.51 (d, J = 16.5Hz, 6H): -C(C<u>H</u>$_3$)$_2$-P

1.47 (t, J = 7Hz, 6H): arom. O-CH$_2$-C<u>H</u>$_3$

Example 5: Dimethyl 4-(4,5-dimethoxy-3-hydroxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate



The procedure described in the preceding example was followed, using 4,5-di-methoxy-3-hydroxybenzaldehyde (1.2 g, 6.6 mmol). The crude compound obtained was purified by flash column chromatography (SiO_2, 98/2 AcOEt/MeOH). An amount of 0.72 g (2.0 mmol, 30 % yield) of the title compound was obtained.

MS: m/e = 358: M^+, 248: M^+ - HPO_3Me_2, 207 (100%): M^+- $CMe_2(PO_3Me_2)$

NMR: ($CDCl_3$)

δ = 7.57 (d, J = 15.5Hz, 1H): Ph-C<u>H</u>=CH

7.28 (d, J = 15.5Hz, 1H): Ph-CH=C<u>H</u>

6.95 and 6.69 (two d, J = 2Hz, 2H): arom. H

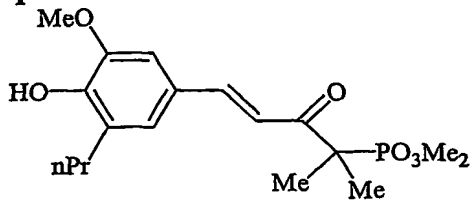
6.15 (s, 1H): OH

3.92 (d, J = 11 Hz, 6H): P-O-C<u>H</u>$_3$

3.81 and 3.79 (two s, 6H): arom. O-C<u>H</u>$_3$

1.51 (d, J = 16.5Hz, 6H): -C(C<u>H</u>$_3$)$_2$-P

Example 6: Dimethyl 4-(4-hydroxy-3-methoxy-5-n-propylphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate



The procedure described in the preceding example was followed, using 4-hydroxy-3-methoxy-5-n-propylbenzaldehyde (1.28 g, 6.6 mmol). The crude compound obtained was purified by flash column chromatography (SiO_2, 98/2 AcOEt/MeOH). An amount of 1.58 g (4.27 mmol, 65 % yield) of the title compound was obtained.

MS: m/e = 370: M^+, 260: M^+ - HPO_3Me_2, 219 (100%): M^+- $CMe_2(PO_3Me_2)$

NMR: ($CDCl_3$)

δ = 7.63 (d, J = 15.5Hz, 1H): Ph-C<u>H</u>=CH

7.27 (d, J = 15.5Hz, 1H): Ph-CH=C<u>H</u>

7.05 and 6.97 (two d, J = 2H, 2H): arom. H

5.98 (s, 1H): OH

3.93 (s, 3H): arom. O-C<u>H</u>$_3$

3.79 (d, J = 11 Hz, 6H): P-O-C<u>H</u>$_3$

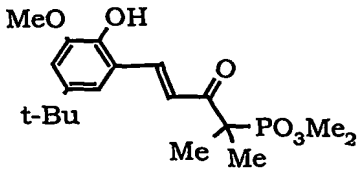
2.62 (q, J = 7 Hz, 2H): arom. C<u>H</u>$_2$-CH_2-CH_3

1.65 (sextet, J = 7 Hz, 2H): arom. CH_2-C<u>H</u>$_2$-CH_3

1.51 (d, J = 16.5Hz, 6H): -C(C<u>H</u>$_3$)$_2$-P

0.97 (t, J = 7 Hz, 3H): arom. CH_2-CH_2-C<u>H</u>$_3$

Example 7: Dimethyl 4-(5-tert-butyl-2-hydroxy-3-methoxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate



To 25 ml dry THF kept at 0°C were added sequentially $TiCl_4$ (2 ml, 18 mmol), 5-tert-butyl-2-hydroxy-3-methoxybenzaldehyde (1.4 g, 6.7 mmol), dimethyl 1,1-dimethyl-2-oxopropylphosphonate (1.6 g, 7.92 mmol), N-methyl morpholine (2.5 ml, 26.4 mmol) then the reaction mixture was stirred for 1 h at room temperature. Work up was carried out by adding 100 ml of iced-water, extracting the resulting mixture with three portions of 100 ml chloroform,

washing the chloroform phase with brine and drying over magnesium sulfate. Evaporation of the solvent gave an oil that was purified by flash column chromatography (SiO_2, 7/3 AcOEt/hexane). An amount of 1.79 g (4.7 mmol, 70 % yield) of the title compound was obtained.

MS: m/e = 384: M^+, 233: M^+- $CMe_2(PO_3Me_2)$, 57: tBu^+

NMR: ($CDCl_3$)

δ = 7.87 (d, J = 15.5Hz, 1H): Ph-C<u>H</u>=CH

7.61 (d, J = 15.5Hz, 1H): Ph-CH=C<u>H</u>

7.10 and 6.92 (2d, 2H): arom. H

6.20 (s, 1H): OH

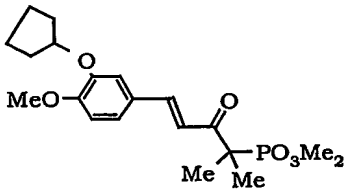
3.93 (s, 1H): arom. O-CH_3

3.80 (d, J = 11 Hz, 6H): P-O-C<u>H</u>$_3$

1.52 (d, J = 16.5Hz, 6H): -C(C<u>H</u>$_3$)$_2$-P

1.32 (s, 9H): t-C_4<u>H</u>$_9$

Example 8: Dimethyl 4-(3-cyclopentyloxy-4-methoxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate



To 50 ml dry THF kept at 0°C were added sequentially $TiCl_4$ (3.0 ml, 27.3 mmol), 3-cyclopentyloxy-4-methoxybenzaldehyde (2 g, 9.1 mmol), dimethyl 1,1-dimethyl-2-oxopropylphosphonate (2.1 g, 10.9 mmol), N-methyl morpholine (3.0 ml, 52.4 mmol) then the reaction mixture was stirred for 1 h at room temperature. Work up was carried out by adding 100 ml of iced-water, extracting the resulting mixture with three portions of 100 ml diethyl ether, washing the ether phase with brine and drying over magnesium sulfate. Evaporation of the solvent gave an oil that was purified by flash column chromatography (SiO_2, pure AcOEt). An amount of 0.92 g (0.25 mmol, 26 % yield) of the title compound was obtained.

MS: m/e = 396: M^+, 177 (100%): M^+- $CMe_2(PO_3Me_2)$ – cC_5H_9

NMR: ($CDCl_3$)

δ = 7.64 (d, J = 15.5Hz, 1H): Ph-C<u>H</u>=CH

7.2 (dd, 1H), 7.10 (d, 1H) and 6.86 (s, 1H): arom. H

7.24 (d, J = 15.5Hz, 1H): Ph-CH=C<u>H</u>

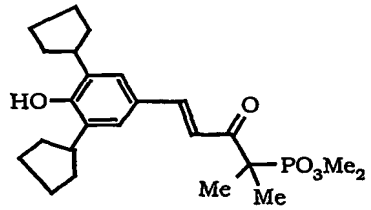
3.88 (s, 3H): O<u>CH</u>$_3$

3.79 and 3.78 (2d, J = 11 Hz, 6H): P-O-<u>CH</u>$_3$

4.82 (septuplet, 2H), 2.0-1.8 (m, 4H), 1.88-1.80 (m, 4H) and 1.65-1.61 (m, 8H): cyclo C_5H_9

1.52 (d, J = 16.7Hz, 6H): -C(<u>CH</u>$_3$)$_2$-P

Example 9: Dimethyl 4-(3,5-dicyclopentyl-4-hydroxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate



To 20 ml dry THF kept at 0°C were added sequentially $TiCl_4$ (0.4 ml, 3.72 mmol), 3,5-di-cyclopentyl-4-hydroxybenzaldehyde (0.4 g, 1.55 mmol), dimethyl 1,1-dimethyl-2-oxopropylphosphonate (0.4 g, 1.86 mmol), N-methyl morpholine (0.9 ml, 7.44 mmol) then the reaction mixture was stirred for 1 h at room temperature. Work up was carried out by adding 100 ml of iced-water, extracting the resulting mixture with three portions of 100 ml diethyl ether, washing the ether phase with brine and drying over magnesium sulfate. Evaporation of the solvent gave an oil that was purified by flash column chromatography (SiO_2, 7/3 AcOEt/hexane). An amount of 0.14 g (0.32 mmol, 21 % yield) of the title compound was obtained.

MS: m/e = 434: M^+, 283 (100%): M^+- $CMe_2(PO_3Me_2)$

NMR: ($CDCl_3$)

δ = 7.66 (d, J = 15.5Hz, 1H): Ph-C<u>H</u>=CH

7.31 (s, 2H): arom. H

7.42 (d, J = 15.5Hz, 1H): Ph-CH=C<u>H</u>

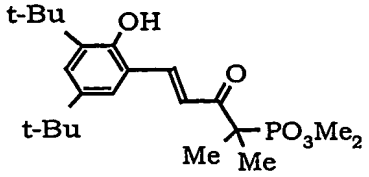
ca 5.3: O<u>H</u>

3.84 and 3.78 (2d, J = 11 Hz, 6H): P-O-<u>CH</u>$_3$

3.17 (quintet, 2H), 2.1-2.03 (m, 4H), 1.88-1.80 (m, 4H) and 1.75-1.61 (m, 8H): cyclo C_5H_9

1.52 (d, J = 16.7Hz, 6H): -C(<u>CH</u>$_3$)$_2$-P

Example 10: Dimethyl 4-(3,5-di-tert-butyl-2-hydroxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate



To 30 ml dry THF kept at 0°C were added sequentially $TiCl_4$ (2.9 g, 15.5 mmol), 3,5-di-tert-butyl-2-hydroxybenzaldehyde (1.55 g, 6.54 mmol), dimethyl 1,1-dimethyl-2-oxopropylphosphonate (1.6 g, 7.83 mmol), N-methyl morpholine (2.5 ml, 3.12 g, 30.9 mmol) then the reaction mixture was stirred for 2h at 0°C. Work up as previously described and purification by flash column chromatography (SiO_2, 98/2 CH2Cl2/MeOH) gave 0.87 g (2.2 mmol, 32 % yield) of the title compound. Recrystallization from a mixture of petroleum ether and dichloromethane gave a white solid, mp= 142-144°C.

MS: m/e= 410: M^+, 259 (27%): M^+- $CMe_2(PO_3Me_2)$, 57 : tBu^+, 152 (100%): $CHMe_2(PO_3Me_2)^+$

NMR: ($CDCl_3$)

δ = 7.92 (d, J = 15.5Hz, 1H): Ph-C<u>H</u>=CH

7.35 (d, J = 15.5Hz, 1H): Ph-CH=C<u>H</u>

7.37 and 7.30 (two d, J = 2Hz, 2H): arom. H

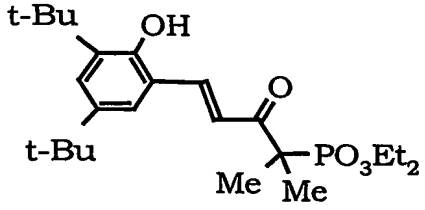
5.98 (broad s, 1H): phenol O<u>H</u>

3.80 (d, J = 11Hz, 6H): P-O-C<u>H</u>$_3$

1.52 (d, 16.5Hz, 6H): -C(C<u>H</u>$_3$)$_2$-P

1.45 and 1.31 (two s, 9H each): t-C$_4$<u>H</u>$_9$

Example 11: Diethyl 4-(3,5-di-tert-butyl-2-hydroxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate



To 30 ml dry THF kept at 0°C were added sequentially $TiCl_4$ (7.79 g, 41.03 mmol), 3,5-di-tert-butyl-2-hydroxybenzaldehyde (4.0 g, 17.09 mmol), diethyl 1,1-dimethyl-2-oxopropylphosphonate 4.55 g, 20.51 mmol), N-methyl morpholine (8.29 g, 82.05 mmol) then the reaction mixture was stirred for 2 h at 0°C. Work up as previously described and purification by

flash column chromatography (SiO_2, 98/2 CH2Cl2/MeOH) gave 0.87 g (1.96 mmol, 13 % yield) of the title compound. Recrystallization from a mixture of petroleum ether and dichloromethane gave a white solid, mp= 94-95°C.

MS: m/e = 438: M^+, 259 (32%): M^+- $CMe_2(PO_3Et_2)$, 180 (100%): $CMe_2(PO_3Et_2)^+$, 57: tBu^+

NMR: ($CDCl_3$)

δ = 7.89 (d, J = 15.5Hz, 1H): Ph-C<u>H</u>=CH

7.37 (d, J = 15.5Hz, 1H): Ph-CH=C<u>H</u>

7.36 and 7.29 (two d, J = 2Hz, 2H): arom. H

5.98 (broad s, 1H): phenol O<u>H</u>

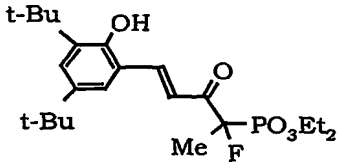
4.19-4.12 (m, 4H): P-O- C<u>H_2</u>-CH_3

1.52 (d, 16.5Hz, 6H): -C($C\underline{H_3}$)$_2$-P

1.44 and 1.31 (two s, 9H each): t-$C_4\underline{H_9}$

1.33 (t, J = 7Hz, 6H): P-O- CH_2-C<u>H_3</u>

Example 12: Diethyl 4-(3,5-di-tert-butyl-2-hydroxyphenyl)-1-fluoro-1-methyl-2-oxo-3-buten-1-yl-phosphonate



To a suspension of sodium hydride (0.77g of a 60% suspension in mineral oil, 32.05 mmol) in 60 ml THF was added a solution of 3,5-di-tert-butyl-2-hydroxybenzaldehyde (3.0 g, 12.82 mmol) in 10 ml THF and the resulting mixture was stirred for 30 min at 0°C. 2-Methoxyethoxymethyl chloride (3.19 g, 25.64 mmol) was added dropwise and the resuting mixture was stirred for 4 h at room temperature. After hydrolysis by a saturated NH4Cl solution, the reaction mixture was partitioned between water and DCM. The dried organic phase was evaporated and the residue was purified by column chromatography (SiO2, DCM) to give 2.5 g of 3,5-di-tert-butyl-2-(2-methoxyethoxymethoxy) benzaldehyde (7.8 mmol, 61%).

To a suspension of sodium hydride (0.93g of a 60% suspension in mineral oil, 38.82 mmol) in 60 ml THF was added a solution of triethyl phosphonoacetate (3.48 g, 15.53 mmol) in 10 ml THF and the resulting mixture was stirred for 30 min at 0°C. 3,5-di-tert-butyl-2-(2-methoxyethoxymethoxy)benzaldehyde (2.5 g, 7.8 mmol) was added dropwise and the resuting mixture was stirred for 2 h at room temperature. After hydrolysis by a saturated NH4Cl solution, the reaction mixture was partitioned between water and DCM. The dried organic phase was

evaporated and the residue was purified by column chromatography (SiO2, 98/2 DCM/MeOH) to give 2.1 g of ethyl 3,5-di-tert-butyl-2-(2-methoxyethoxymethoxy)cinnamate (5.4 mmol, 68%).

n-Butyllithium (9.6 ml of a 1.6 M solution in hexane, 15.31 mmol) was added to 80 ml of THF cooled to –78°C, followed by diethyl ethylphosphonate (2.54 g, 15.31 mmol). The resulting solution was stirred for 15 min at –78°C, then a solution of ethyl 3,5-di-tert-butyl-2-(2-methoxyethoxymethoxy) cinnamate (2 g, 5.10 mmol) in 10 ml THF was added and the resulting reaction was left to stir at –78°C for 1 h. A saturated NH4Cl solution was added, the separated THF phase was collected and the aqueous phase was extracted with DCM. The THF and DCM portions were pooled, reextracted with brine, dried over MgSO4 and evaporated. The residue was purified by column chromatography (SiO2, 98/2 DCM/MeOH) to give 2.2 g (4.3 mmol, 82 %) of diethyl 4-[3,5-di-tert-butyl-2-(2-methoxyethoxymethoxy)phenyl]-1-methyl-2-oxo-3-buten-1-ylphosphonate.

A solution of diethyl 4-[3,5-di-tert-butyl-2-(2-methoxyethoxymethoxy)phenyl]-1-methyl-2-oxo-3-buten-1-ylphosphonate (1.1 g, 2.15 mmol) dissolved in 10 ml MeCN was added to a suspension of sodium ethoxide (0.31 g, 4.51 mmol) in 50 ml MeCN kept at 0°C, the reaction was left to stir for 15 min then 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (1.6 g, 4.51 mmol) was added portionwise and the reaction mixture was left to stir at room temperature for 15 min. Water was added, the mixture was extracted into DCM. The organic solution was extracted with brine, dried over MgSO4 and evaporated. The residue containing 1.1 g (2.07 mmol, 96% crude) of diethyl 2-[3,5-di-tert-butyl-4-(2-methoxyethoxymethoxy) phenyl]-1-fluoro-1-methyl-2-oxo-3-buten-1-ylphosphonate.

A mixture containing the latter compound (0.45 g, 0.89 mmol) was dissolved in a mixture of TFA (1.19 g, 10.4 mmol) in 15 ml dichloromethane was stirred at room temperature for 1h. A 10% sodium hydroxide solution was added until pH 6, the aqueous solution extracted with dichloromethane, dried and evaporated to dryness. Purification by column chromatography (SiO2, 8/2 Hexane/AcOEt) gave 0.28 g (0.63 mmol, 30 %) of diethyl 4-(3,5-di-tert-butyl-2-hydroxyphenyl)-1-fluoro-1-methyl-2-oxo-3-buten-1-ylphosphonate.

MS:m/e= 442: M^+, 259 (56%): M^+- CMeF-(PO_3Et_2), 184 (100%): HCMeF-$(PO_3Et_2)^+$, 57: tBu^+

NMR: ($CDCl_3$)

δ = 7.31 and 7.03 (two d, J = 2.4Hz, 2H): arom. H

6.79 (two d, J = 9.7Hz, 1H): Ph-C<u>H</u>=CH

6.00 (d, J = 9.7Hz, 1H): Ph-CH=C<u>H</u>

6.50 (broad s, 1H): phenol O<u>H</u>

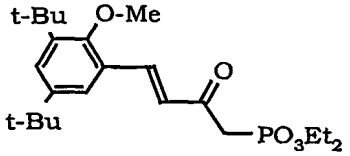
4.42-4.25 (m, 4H): P-O- $C\underline{H}_2$-CH_3

1.63(dd, J= 24.6Hz and 13.8 Hz, 3H): -CF($C\underline{H}_3$) -P

1.46 and 1.30(two s, 9H each): t-$C_4\underline{H}_9$

1.33 (two overlapped t, J = 7Hz, 6H) : P-O- CH_2-$C\underline{H}_3$

Example 13: Diethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-2-oxo-3-buten-1-yl phosphonate



A mixture of 3,5-di-tert-butyl-2-methoxybenzaldehyde (5g, 20.16 mmol), ethyl hydrogen malonate (7.45 g, 56.45 mmol), pyridine (7.52 ml, 93 mmol) and piperidine (0.39 ml, 4.03 mmol) was heated at 110°C for 12 h. Pyridine was removed by vacuum distillation then to the residue were added a few drops of 10% HCl to bring the pH to ca 5. The neutralised mixture was extracted with chloroform (three 50 ml portions), the separated organic phase was added to 100 ml of a sodium hydroxide solution (pH = 10) and the resulting mixture was heated for 15 min. The chloroform phase was separated, the aqueous phase further extracted with fresh chloroform, the combined chloroform phases were dried, evaporated to dryness. The residue was purified by column chromatography (SiO2, dichloromethane (DCM)) to give 4.0 g (12.5 mmol, 62%) of ethyl 3,5-di-tert-butyl-2-methoxycinnamate.

Under nitrogen atmosphere diethyl methylphosphonate (3.04 g, 19.97 mmol) was added at -78° to a solution of n-butyllithium (12.5 ml of a 1.6 M solution in hexane, 19.97 mmol) in 70 ml anhydrous THF. The reaction mixture was stirred at -78° for 30 min to allow for complete formation of the lithium anion. The mixture was again cooled to -78° and a solution of ethyl 3,5-di-tert-butyl-2-methoxycinnamate (2.54 g, 7.99 mmol) in 20 ml dry THF was added. The resulting orange-colored mixture was left to stir at room temperature (25°C) for 2 h. Hydrolysis was carried out by adding 10 ml of a 10% HCl solution and the product was extracted into ether, dried over $MgSO_4$ and evaporated. The residue was purified by column choromatography (SiO2, 98/2 DCM/MeOH) to yield a yellow viscous oil (1.2 g, 2.83 mmol, 59% yield) of diethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-2-oxo-3-buten-1-yl phosphonate.

MS (m/e): 424: M^+, 393 (100%): M+ -OMe, 367: M+ -tBu, 57 (100%): tBu

NMR ($CDCl_3$)

δ = 7.94 (d, J = 16 Hz, 1H): Ph-C$\underline{H}$=CH

7.43 (s, 1H): arom. H

6.87 (d, J = 16Hz, 1H): Ph-CH=C<u>H</u>

4.23-4.13 (m, 4H): P-O-C<u>H</u>$_2$-CH$_3$

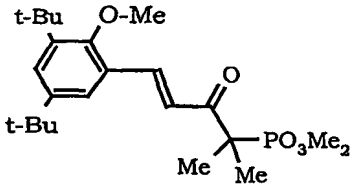
3.80: OC<u>H</u>$_3$

3.37 (d, J = 23 Hz, 2H): C<u>H</u>$_2$-P

1.41 and 1.32 (2s, 9H each): t-C$_4$<u>H</u>$_9$

1.34 (t, J = 7Hz, 6H): P-O-CH$_2$-C<u>H</u>$_3$

Example 14: Dimethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate



Methyl iodide (2.7 ml, 6.1 g, 43 mmol) was added dropwise to a mixture of 3,5-di-tert-butyl-2-hydroxybenzaldehyde (5.0 g, 21.3 mol), potassium carbonate (4.4 g, 32 mmol), tetra-n-butylammonium bromide (0.69 g, 2.1 mmol) dissolved in 100 ml of 2-butanone and the resulting mixture was refluxed for 3 h.

Further portions of methyl iodide were added (4 X 3 ml) at regular intervals and refluxing was resumed to complete the conversion. The cooled mixture was filtered, the filtrate was concentrated under vacuum and partitioned between dichloromethane and water. Evaporation of the dried organic phase gave 5.3 g (22.4 mmol, 101% crude) of 3,5-di-tert-butyl-2-methoxybenzaldehyde.

To 30 ml dry THF kept at 0°C were added sequentially $TiCl_4$ (1.1 ml, 9.78 mmol), 3,5-di-tert-butyl-2-methoxybenzaldehyde (1.0 g, 4.03 mmol), dimethyl 1,1-dimethyl-2-oxopropylphosphonate (0.94 g, 4.84 mmol), N-methyl morpholine (1.96 g, 19.4 mmol) then the reaction mixture was stirred for 4h at room temperature. Work up as previously described and purification by flash column chromatography (SiO_2, 95/5 AcOEt/hexane) gave 0.3 g (0.71 mmol, 18 % yield) of the title compound.

MS: m/e = 424: M^+, 393 (100%): M^+ - OMe, 273: M^+- $CMe_2(PO_3Me_2)$, 57: tBu^+

NMR: ($CDCl_3$)

δ = 7.97 (d, J = 15.7Hz, 1H): Ph-C<u>H</u>=CH

7.45 and 7.41 (2d, 2H): arom. H

7.38 (d, J = 15.5Hz, 1H): Ph-CH=C<u>H</u>

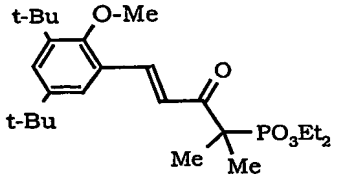
3.80 (d, J = 11 Hz, 6H): P-O-C$\underline{H}_3$

3.77 (s, 3H): O-Me

1.53 (d, J = 16.5Hz, 6H): -C(C$\underline{H}_3$)$_2$-P

1.41 and 1.33 (2s, 9H each): t-C$_4\underline{H}_9$

Example 15: Diethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate



The method described for the preceding example SR-163106 was followed, using the reactants in the following amounts: THF (15 ml), $TiCl_4$ (0.8 ml, 7.26 mmol), 3,5-di-tert-butyl-2-methoxybenzaldehyde (0.75 g, 3.03 mmol), diethyl 1,1-dimethyl-2-oxopropyl phosphonate (0.8 g, 3.63 mmol), N-methyl morpholine (1.6 ml, 14.5 mmol). An amount of 0.8 g (1.77 mmol, 58 % yield) of the title compound was obtained.

MS: m/e = 452: M^+, 451 (100%): M^+ - OMe, 273: M^+- $CMe_2(PO_3Et_2)$, 57: tBu^+

NMR: ($CDCl_3$)

δ = 7.97 (d, J = 15.7Hz, 1H): Ph-C$\underline{H}$=CH

7.45 and 7.40 (2d, 2H): arom. H

7.44 (d, J = 15.7 Hz, 1H): Ph-CH=C$\underline{H}$

4.19-4.11 (m, 4H): P-O-C$\underline{H}_2$-CH_3

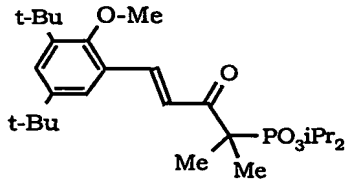
3.76 (s, 3H): O-Me

1.52 (d, J = 16.5Hz, 6H): -C(C$\underline{H}_3$)$_2$-P

1.40 and 1.33 (2s, 9H each): t-C$_4\underline{H}_9$

1.33 (t, 7Hz, 6H): P-O-CH_2-C$\underline{H}_3$

Example 16: Diisopropyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate



The method described for the preceding example SR-163106 was followed, using the reactants in the following amounts: THF (15 ml), $TiCl_4$ (0.8 ml, 7.26 mmol), 3,5-di-tert-butyl-2-methoxybenzaldehyde (0.75 g, 3.03 mmol), diisopropyl 1,1-dimethyl-2-oxopropyl phosphonate (0.9 g, 3.63 mmol), N-methyl morpholine (1.6 ml, 14.5 mmol). An amount of 1.08 g (2.08 mmol, 68 % yield) of the title compound was obtained.

MS: m/e = 480: M^+, 449 (86%): M^+ - OMe, 273: M^+- $CMe_2(PO_3iPr_2)$, 57: tBu^+

NMR: ($CDCl_3$)

δ = 7.95 (d, J = 15.7Hz, 1H): Ph-C<u>H</u>=CH

7.45 and 7.40 (2d, J= 2.4Hz, 2H): arom. H

7.44 (d, J = 15.7Hz, 1H): Ph-CH=C<u>H</u>

4.74 (m, 2H): P-O-C<u>H</u>-$(CH_3)_2$

3.76 (s, 3H): O-Me

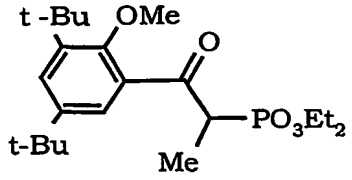
1.49 (d, J = 16.5Hz, 6H): -C($C\underline{H}_3$)$_2$-P

1.40 and 1.33 (2s, 9H each): t-$C_4\underline{H}_9$

1.33 and 1.32 (2d, 6Hz, 6H each): P-O-CH-($C\underline{H}_3$)$_2$

1.33 and 1.32 (2d, 7Hz, 6H each): P-O-CH-($C\underline{H}_3$)$_2$

Example 17: Diethyl 2-(3,5-di-tert-butyl-2-methoxyphenyl)-1-methyl-2-oxo-ethylphosphonate



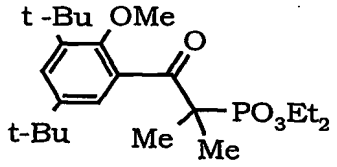
A solution of 5.74 g (36.3 mmol) potassium permanganate in 115 ml water was added to a mixture of 6.44 g (25.9 mmol) in 160 ml water heated to 75°C. Heating was continued for a further hour then the reaction mixture was basified with 10% sodium hydroxide, filtered hot over a Buchner funnel and rinsed with hot water. The combined filtrates were cooled and acidified with 10% HCl. A fine precipitate was formed which was extracted into chloroform. The dried organic phase was evaporated to give 3.8 g (55%) of a colorless solid.

A 80 ml methanol solution containing 4.0 g (15.1 mmol) of the 3,5-di-tert-butyl-2-methoxybenzoic acid thus formed and 8 ml concentrated sulfuric acid was heated to reflux for 5h. The cooled solution was neutralized with a saturated sodium bicarbonate solution, methanol

was evaporated then the residue was basified to pH 10 with 10% sodium hydroxide. The aqueous emulsion was extracted with chloroform, the organic phase was washed with sodium bicarbonate, dried and evaporated to yield 3.89 g (14.0 mmol, 93%) of methyl 3,5 di-tert-butyl-2-methoxybenzoate as a light brown oil.

n-Butyllithium (9.3 ml of a 1.6 M solution in hexane, 14.9 mmol) was added to 20 ml of THF cooled to –78°C, followed by diethyl ethylphosphonate (2.15 g, 12.9 mmol). The resulting solution was stirred for 15 min at –78°C, then a solution of methyl 3,5-di-tert-butyl-2-methoxybenzoate (1.8 g, 6.47 mmol) in 5 ml THF was added and the resulting reaction was left to reach room temperature over 2 h. A saturated NH_4Cl solution was added, the separated THF phase was collected and the aqueous phase was extracted with 3 portions of diethyl ether. The THF and ether portions were pooled, extracted with brine, dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography (SiO_2, 2/8 AcOEt/hexane) to give 2.36 g (5.72 mmol, 88 %) of the title compound as a yellow oil.

Example 18: Diethyl 2-(3,5-di-tert-butyl-2-methoxyphenyl)-1,1-dimethyl-2-oxo-ethylphosphonate



A solution of diethyl 2-(3,5-di-tert-butyl-2-methoxyphenyl)-1-methyl-2-oxo-ethylphosphonate (2.36 g, 5.92 mmol) dissolved in 7 ml THF was added to a suspension of sodium hydride (0.47 g of a 60% dispersion in mineral oil, 11.8 mmol) in 20 ml THF kept at 0°C, the reaction was left to stir for 15 min then methyl iodide (0.74 ml, 11.9 mmol) was added and the reaction mixture was left to stir at room temperature for 2h. Water was added, the separated THF phase was collected and the aqueous phase was extracted with 3 portions of dichloromethane. The THF and DCM portions were pooled, extracted with brine, dried over MgSO4 and evaporated. The residue was purified by column chromatography (SiO_2, 95/5 DCM/MeOH) to give 1.03 g (2.41 mmol, 41 %) of the title compound.

MS: m/e= 426: M^+ , 247 (62%): M^+-$C(CH_3)_2$-PO_3Et_2, 57 (100%): tBu^+

NMR: ($CDCl_3$)

δ = 7.34 and 7.13 (2d, 1H each): arom. H

4.21-4.15 (m, 4H): P-O-$C\underline{H}_2$-CH_3

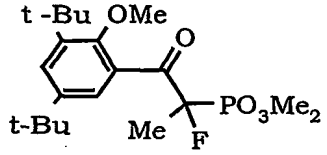
3.66 (1s, 3H): arom. O-$C\underline{H}_3$

1.49 (d, J = 16.5 Hz, 6H): -C($C\underline{H}_3$)$_2$-P

1.38 and 1.30 (2s, 9H each): t-$C_4\underline{H}_9$

1.34 (t, J = 7Hz, 6H): P-O-CH_2-$C\underline{H}_3$

Example 19: Dimethyl 2-(3,5-di-tert-butyl-2-methoxyphenyl)-1-fluoro-1-methyl-2-oxo-ethylphosphonate



A solution of dimethyl 2-(3,5-di-tert-buty-2-methoxylphenyl)-1-methyl-2-oxo-ethylphosphonate (0.5 g, 1.3 mmol) dissolved in 5 ml THF was added to a suspension of sodium hydride (0.06 g of a 60% dispersion in mineral oil, 1.56 mmol) in 10 ml THF kept at 0°C, the reaction was left to stir for 15 min then 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo [2.2.2] octane bis(tetrafluoroborate) (0.5 g, 1.5 mmol) was added and the reaction mixture was left to stir at room temperature for 2 h. Water was added, the separated THF phase was collected and the aqueous phase was extracted with 3 portions of DCM. The THF and DCM portions were pooled, extracted with brine, dried over MgSO4 and evaporated. The residue was purified by column chromatography (SiO_2, 98/2 $CHCl_3$/MeOH) to give 0.12 g (0.3 mmol, 22%) of the title compound.

MS: 402: M^+, 247 (100%): M+ - C(F)(Me)PO_3Me_2

NMR: ($CDCl_3$)

δ = 7.47 (d, 1H) and 7.45 (t, 1H): arom. H

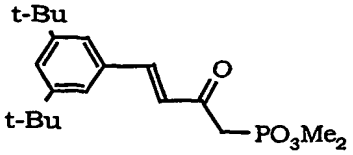
3.90 and 3.83 (2 d,J = 10.7 Hz, 6H): P-O-$C\underline{H}_3$

3.72 (s, 3H): arom. O-$C\underline{H}_3$

1.98 (dd, J = 24.1 and 15.3 Hz, 3H): -CF($C\underline{H}_3$)-P

1.41 and 1.32 2(s, 9H each): t-$C_4\underline{H}_9$

Example 20: Dimethyl 4-(3,5-di-tert-butylphenyl)-2-oxo-3-buten-1-yl phosphonate



A mixture of 3,5-di-tert-butylbenzaldehyde (5g, 22.94 mmol), ethyl hydrogen malonate (8.48 g, 64.22 mmol), pyridine (8.64 ml, 105 mmol) and piperidine (0.45 ml, 4.59 mmol) was heated at 110°C for 12 h. Pyridine was removed by vacuum distillation then to the residue were added a few drops of 10% HCl to bring the pH to ca 5. The neutralised mixture was extracted with chloroform (three 50 ml portions), the separated organic phase was added to 100 ml of a sodium hydroxide solution (pH = 9) and the resulting mixture was heated for 15 min. The chloroform phase was separated, the aqueous phase further extracted with fresh chloroform, the combined chloroform phases were dried, evaporated to dryness. The residue was purified by column chromatography (SiO2, AcOEt/MeOH 9/1) to give 4.7 g (16.3 mmol, 71%) of ethyl 3,5-di-tert-butylcinnamate.

Under nitrogen atmosphere dimethyl methylphosphonate (2.37 g, 19 mmol) was added at –78°C to a solution of n-butyllithium (12 ml of a 1.6 M solution in hexane, 19.2 mmol) in 50 ml anhydrous THF. The reaction mixture was stirred at -70° for 30 min to allow for complete formation of the lithium anion (slight turbidity). A solution of ethyl 3,5-di-tert-butylcinnamate (2.2 g, 7.64 mmol) in 5 ml dry THF was added. The resulting mixture was left to stir at room temperature (25°C) for 4 h. Hydrolysis was carried out by adding 10 ml of a 10% HCl solution and the product was extracted into chloroform. After drying over $MgSO_4$, chloroform was evaporated and the residue was purified by column chromatography (SiO2, AcOEt/hexane 8/2) to give 2 g (5.45 mmol, 72%) of the title compound.

MS (m/e): 366 M^+, 351: M^+-Me, 309: M^+ - tBu, 256: M^+-HPO_3Me_2, 57: tBu^+

NMR ($CDCl_3$)

δ = 7.67 (d, J = 16Hz, 1H): Ph-C<u>H</u>=CH

7.51 (t, 1H) and 7.42 (d, 2H): arom. H

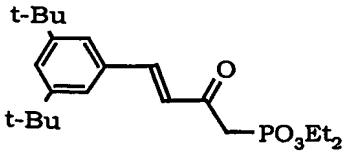
6.86 (d, J = 16 Hz, 1H): Ph-CH=C<u>H</u>

3.82 (d, J = 11Hz, 6H): P-O-C<u>H</u>$_3$

3.37 (d, J = 22Hz, 2H: C<u>H</u>$_2$-P

1.35 (s, 18H): t-C_4<u>H</u>$_9$

Example 21: Diethyl 4-(3,5-di-tert-butylphenyl)-2-oxo-3-buten-1-yl phosphonate



Under nitrogen atmosphere diethyl methylphosphonate (3.3 g, 21.7 mmol) was added at -78° to a solution of n-butyllithium (13.6 ml of a 1.6 M solution in hexane, 21.7 mmol) in 75 ml anhydrous THF. The reaction mixture was stirred at -78° for 30 min to allow for complete formation of the lithium anion. The mixture was again cooled to -60° and a solution of ethyl 3,5-di-tert-butylcinnamate (2.5 g, 8.68 mmol) in 20 ml dry THF was added. The resulting orange-colored mixture was left to stir at room temperature (25°C) for 2 h. Hydrolysis was carried out by adding 10 ml of a 10% HCl solution and the product was extracted into ether. After drying over $MgSO_4$, ether was evaporated to yield a yellow solid (2.8 g, 7.1 mmol, 81 % yield) of diethyl 4-(3,5-di-tert-butylphenyl)-2-oxo-3-buten-1-yl phosphonate. Mp=90-91°C

MS (m/e): 394: M^+, 379: M+ -Me, 337: M+ -tBu, 256: M^+-HPO_3Et_2, 57 (100%): tBu

NMR ($CDCl_3$)

δ = 7.67 (d, J = 16 Hz, 1H): Ph-C<u>H</u>=CH

7.50 (t, 1H) and 7.42 (d, 2H): arom. H

6.88 (d, J = 16Hz, 1H): Ph-CH=C<u>H</u>

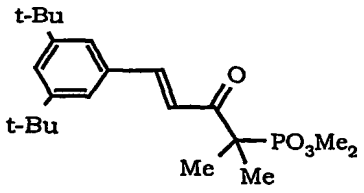
4.22-4.11 (m, 4H): P-O-C<u>H</u>$_2$-CH$_3$

3.36 (d, J = 23 Hz, 2H): C<u>H</u>$_2$-P

1.35 (s, 18H): t-C$_4$<u>H</u>$_9$

1.35 (t, J = 7Hz, 6H): P-O-CH$_2$-C<u>H</u>$_3$

Example 22: Dimethyl 4-(3,5-di-tert-butylphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate



To 50 ml dry THF kept at 0°C were added sequentially $TiCl_4$ (3.6 ml, 32.5 mmol), 3,5-di-tert-butylbenzaldehyde (1.0 g, 4.6 mmol), dimethyl 1,1-dimethyl-2-oxopropylphosphonate (1.2 g, 5.95 mmol), N-methyl morpholine (1.85 g, 18.5 mmol) then the reaction mixture was stirred for 1 h at room temperature. Work up was carried out by adding 100 ml of iced-water, extracting the resulting mixture with three portions of 100 ml diethyl ether, washing the ether phase with brine and drying over magnesium sulfate. Evaporation of the solvent gave an oil that was purified by flash column chromatography (SiO_2, 1/1 AcOEt/hexane). An amount of 1.0 g (2.53 mmol, 56 % yield) of the title compound was obtained, mp = 50-52°C.

MS: m/e = 395: $M^+ + 1$, 243 (100%): M^+- $CMe_2(PO_3Me_2)$, 57: tBu^+

NMR: ($CDCl_3$)

δ = 7.77 (d, J = 15.6Hz, 1H): Ph-C<u>H</u>=CH

7.53 (t, 1H) and 7.48 (d, 2H): arom. H

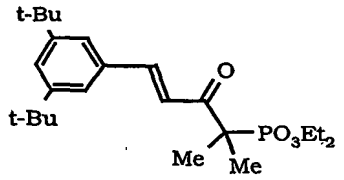
7.42 (d, J = 15.6Hz, 1H): Ph-CH=C<u>H</u>

3.84 and 3.78 (2d, J = 11 Hz, 6H): P-O-C<u>H</u>$_3$

1.57 (d, J = 16.7Hz, 6H): -C(C<u>H</u>$_3$)$_2$-P

1.39 (s, 18H): t-C$_4$<u>H</u>$_9$

Example 23: Diethyl 4-(3,5-di-tert-butylphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate



The method described for the preceding example was followed, using the reactants in the following amounts: THF (10 ml), $TiCl_4$ (0.8 g, 4.14 mmol), 3,5-di-tert-butylbenzaldehyde (0.3 g, 1.38 mmol), diethyl 1,1-dimethyl-2-oxopropyl phosphonate (0.4 g, 1.8 mmol), N-methyl morpholine (0.56 g, 5.52 mmol). An amount of 0.52 g (1.23 mmol, 89 % yield) of the title compound was obtained.

MS: m/e = 423: $M^+ + 1$, 243 (100%): M^+- $CMe_2(PO_3Et_2)$, 57: tBu^+

NMR: ($CDCl_3$)

δ = 7.75 (d, J = 16Hz, 1H): Ph-C<u>H</u>=CH

7.53 (t, 1H) and 7.48 (d, 2H): arom. H

7.45 (d, J = 16Hz, 1H): Ph-CH=C<u>H</u>

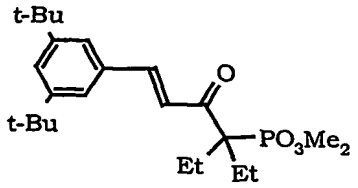
4.19 (m, 4H): P-O-C<u>H</u>$_2$-CH$_3$

1.56 (d, J = 17Hz, 6H): -C(C<u>H</u>$_3$)$_2$-P

1.39 (s, 18H): t-C$_4$<u>H</u>$_9$

1.37 (t, J = 7Hz, 6H): P-O-CH$_2$-C<u>H</u>$_3$

Example 24: Dimethyl 4-(3,5-di-tert-butylphenyl)-1,1-diethyl-2-oxo-3-buten-1-yl-phosphonate



MS: m/e = 423: M^++ 1, 243 (100%): M^+- $C(Et)_2(PO_3Me_2)$, 57 : tBu^+

NMR: ($CDCl_3$)

δ = 7.72 (d, J = 15.5Hz, 1H): Ph-C<u>H</u>=CH

7.49 (t, 1H) and 7.43 (d, 2H): arom. H

7.37 (d, J = 15.5Hz, 1H): Ph-CH=C<u>H</u>

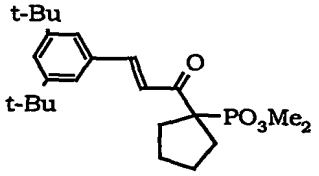
3.79 (d, J = 11 Hz, 6H): P-O-C<u>H</u>$_3$

2.08 (m, 4H): -C(C<u>H</u>$_2$-CH$_3$)$_2$-P

1.36 (s, 18H): t-C$_4$<u>H</u>$_9$

0.98 (t, J = 7 Hz, 6H): -C(CH$_2$-C<u>H</u>$_3$)$_2$-P

Example 25: Dimethyl 4-(3,5-di-tert-butylphenyl)-1,1-cyclopentyliden-2-oxo-3-buten-1-yl-phosphonate



MS: m/e = 420: M^+, 243 (100%): M^+- (c-C_5H_8)(PO_3Me_2), 57: tBu^+

NMR: ($CDCl_3$)

δ = 7.73 (d, J = 15.5Hz, 1H): Ph-C<u>H</u>=CH

7.49 (t, 1H) and 7.43 (d, 2H): arom. H

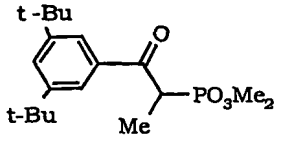
7.30 (d, J = 15.5Hz, 1H): Ph-CH=C<u>H</u>

3.79 (d, J = 11 Hz, 6H): P-O-C<u>H</u>$_3$

2.47, 2.20, 1.74 and 1.55 (4m, 2H each): -(c-C$_5$<u>H</u>$_8$)-P

1.35 (s, 18H): t-C$_4$<u>H</u>$_9$

Example 26: Dimethyl 2-(3,5-di-tert-butylphenyl)-1-methyl-2-oxo-ethylphosphonate



n-Butyllithium (11.5 ml of a 1.6 M solution in hexane, 18.4 mmol) was added to 40 ml of THF cooled to –78°C, followed by dimethyl ethylphosphonate (3.94 g, 28.5 mmol). The resulting solution was stirred for 15 min at –78°C, then a solution of ethyl 3,5-di-tert-butylbenzoate (2.5 g, 9.6 mmol) in 10 ml THF was added and the resulting reaction was left to gradually reach room temperature overnight. A saturated ammonium chloride solution was added, the separated THF phase was collected and the aqueous phase was extracted with 3 portions of ethyl ether. The THF and ether portions were pooled, extracted with brine, dried over MgSO4 and evaporated. The residue was purified by column chromatography (SiO2, 6/4 AcOEt/hexane) to give 2.36 g (6.67 mmol, 69 %) of the title compound.

MS: m/e= 354: M^+, 217 (100%): M^+- $CH(CH_3)$-PO_3Me_2, 57: tBu

NMR: ($CDCl_3$)

δ = 7.86 (d, 2H) and 7.67 (t, 1H): arom. H

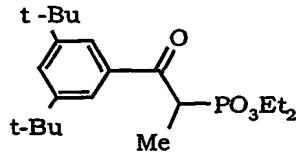
4.23 and 4.19 (2 quartets, J=22.3 Hz, 1H): -C<u>H</u>(CH_3)-P

3.78 and 3.74 (2d, J = 11 Hz, 6H): P-O-C<u>H</u>$_3$

1.56 (dd, J = 18.3 and 7 Hz, 3H): -CH(C<u>H</u>$_3$)-P

1.37 (s, 18H): t-C_4<u>H</u>$_9$

Example 27: Diethyl 2-(3,5-di-tert-butylphenyl)-1-methyl-2-oxo-ethylphosphonate



n-Butyllithium (11.5 ml of a 1.6 M solution in hexane, 18.4 mmol) was added to 40 ml of THF cooled to –78°C, followed by diethyl ethylphosphonate (4.75 g, 28.6 mmol). The resulting solution was stirred for 15 min at –78°C, then a solution of ethyl 3,5-di-tert-butylbenzoate (2.5 g, 9.6 mmol) in 10 ml THF was added and the resulting reaction was left to gradually reach room temperature overnight. A saturated ammonium chloride solution was added, the separated THF phase was collected and the aqueous phase was extracted with 3 portions of diethyl ether. The THF and ether portions were pooled, extracted with brine, dried over MgSO4 and evaporated.

The residue was purified by column chromatography (SiO2, 4/6 AcOEt/hexane) to give 2.32 g (6.0 mmol, 63 %) of the title compound.

MS: m/e= 382: M^+, 217 (100%): M^+-$CH(CH_3)$-PO_3Et_2, 57: tBu

NMR: ($CDCl_3$)

δ = 7.85 (d, 2H) and 7.65 (t, 1H): arom. H

4.20-4.05 (m, 4H): P-O-$C\underline{H}_2$-CH_3

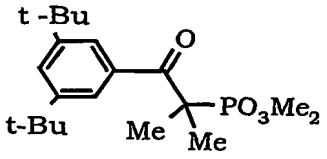
4.20 (overlapped m, 1H): -$C\underline{H}(CH_3)$-P

1.54 (dd, J = 18.1 and 7 Hz, 3H): -$CH(C\underline{H}_3)$-P

1.36 (s, 18H): t-$C_4\underline{H}_9$

1.30 and 1.20 (2t, J = 7Hz, 6H): P-O-CH_2-$C\underline{H}_3$

Example 28: Dimethyl 2-(3,5-di-tert-butylphenyl)-1,1-dimethyl-2-oxo-ethylphosphonate



A solution of dimethyl 2-(3,5-di-tert-butylphenyl)-1-methyl-2-oxo-ethylphosphonate (1.0 g, 2.82 mmol) dissolved in 10ml THF was added to a suspension of sodium hydride (0.23 g of a 60% dispersion in mineral oil, 5.6 mmol) in 20 ml THF kept at 0°C, the reaction was left to stir for 15 min then methyl iodide (1.2 g, 8.5 mmol) was added and the reaction mixture was left to stir at room temperature for 2h. Water was added, the separated THF phase was collected and the aqueous phase was extracted with 3 portions of dichloromethane. The THF and DCM portions were pooled, extracted with brine, dried over MgSO4 and evaporated. The residue was purified by column chromatography (SiO_2, 4/6 AcOEt/hexane) to give 0.6 g (1.94 mmol, 68 %) of the title compound.

MS: m/e= 368: M^+, 217 (100%): M^+- $CH(CH_3)$-PO_3Me_2, 57: tBu^+

NMR: ($CDCl_3$)

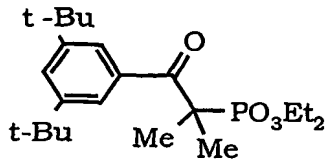
δ = 7.86 (s, 2H) and 7.55 (t, 1H): arom. H

3.80 (d, J = 11 Hz, 6H): P-O-$C\underline{H}_3$

1.60 (d, J = 16.5 Hz, 6H): -$C(C\underline{H}_3)_2$-P

1.36 (s, 18H): t-$C_4\underline{H}_9$

Example 29: Diethyl 2-(3,5-di-tert-butylphenyl)-1,1-dimethyl-2-oxo-ethylphosphonate



A solution of diethyl 2-(3,5-di-tert-butylphenyl)-1-methyl-2-oxo-ethylphosphonate (1.0 g, 2.62 mmol) dissolved in 10ml THF was added to a suspension of sodium hydride (0.26 g of a 60% dispersion in mineral oil, 6.53 mmol) in 15 ml THF kept at 0°C, the reaction was left to stir for 15 min then methyl iodide (1.48 g, 10.5 mmol) was added and the reaction mixture was left to stir at room temperature for 2h. Water was added, the separated THF phase was collected and the aqueous phase was extracted with 3 portions of dichloromethane. The THF and DCM portions were pooled, extracted with brine, dried over MgSO4 and evaporated. The residue was purified by column chromatography (SiO_2, 2/3 AcOEt/hexane) to give 0.65 g (1.7 mmol, 65 %) of the title compound.

MS: m/e= 396: M^+, 217 (100%): M^+- C $(CH_3)_2$ -PO_3Et_2, 57: tBu^+

NMR: ($CDCl_3$)

δ = 7.85 (d, 2H) and 7.54 (t, 1H): arom. H

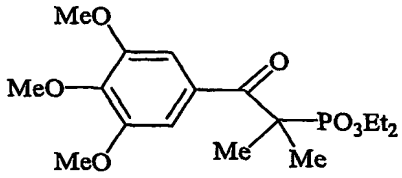
4.20-4.10 (m, 4H): P-O-C<u>H</u>$_2$ –CH_3

1.58 (d, J = 16.5 Hz, 6H): -C(C<u>H</u>$_3$)$_2$-P

1.35 (s, 18H): t-C_4<u>H</u>$_9$

1.30 (t, J=7 Hz, 6H): P-O-CH_2 –C<u>H</u>$_3$

Example 30: Diethyl 2-(3,4,5-trimethoxyphenyl)-1,1-dimethyl-2-oxo-ethylphosphonate



The procedure described in the preceding example was followed, using ethyl 3,4,5-trimethoxybenzoate as the starting compound.

MS: m/e= 374: M^+ , 195 (100%): M^+-C$(CH_3)_2$-PO_3Et_2

NMR: ($CDCl_3$)

δ = 7.54 (s, 2H): arom. H

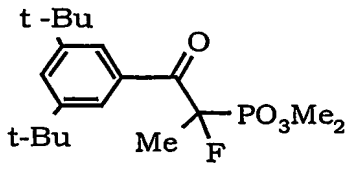
4.15 (m, 4H): P-O-C<u>H</u>$_2$-CH_3

3.91(s, 9H): arom. O-C<u>H</u>$_3$

1.58 (d, J = 16.5 Hz, 6H): -C(C<u>H</u>$_3$)$_2$-P

1.31 (t, J = 7Hz, 6H): P-O-CH$_2$-C<u>H</u>$_3$

Example 31: Dimethyl 2-(3,5-di-tert-butylphenyl)-1-fluoro-1-methyl-2-oxo-ethylphosphonate



A solution of dimethyl 2-(3,5-di-tert-butylphenyl)-1-methyl-2-oxo-ethylphosphonate (1.0 g, 2.82 mmol) dissolved in 10 ml THF was added to a suspension of sodium hydride (0.175 g of a 60% dispersion in mineral oil, 4.35 mmol) in 20 ml THF kept at 0°C, the reaction was left to stir for 15 min then 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (1.3 g, 3.7 mmol) was added and the reaction mixture was left to stir at room temperature for 1 h. Water was added, the separated THF phase was collected and the aqueous phase was extracted with 3 portions of DCM. The THF and DCM portions were pooled, extracted with brine, dried over MgSO4 and evaporated. The residue was purified by column chromatography (SiO_2, 2/3 AcOEt/hexane) to give 0.57 g (1.54 mmol, 59%) of the title compound.

MS: m/e= 372: M^+, 217 (100%): M^+- CF(CH$_3$)-PO$_3$Me$_2$, 57: tBu

NMR: ($CDCl_3$)

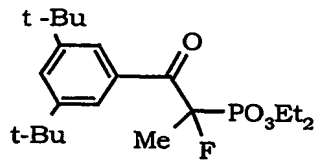
δ = 7.95 (d, J = 1.6 Hz, 2H) and 7.67 (t, 1H): arom. H

3.92 and 3.90 (2 d,J = 10.7 Hz, 6H): P-O-C<u>H</u>$_3$

1.95 (dd, J = 24.1 and 15.3 Hz, 3H): -CF(C<u>H</u>$_3$)-P

1.46 (s, 18H): t-C$_4$<u>H</u>$_9$

Example 32: Diethyl 2-(3,5-di-tert-butylphenyl)-1-fluoro-1-methyl-2-oxo-ethylphosphonate



A solution of diethyl 2-(3,5-di-tert-butylphenyl)-1-methyl-2-oxo-ethylphosphonate (1.0 g, 2.61 mmol) dissolved in 5 ml THF was added to a suspension of sodium hydride (0.21 g of a

60% dispersion in mineral oil, 5.23 mmol) in 15 ml THF kept at 0°C, the reaction was left to stir for 15 min then 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (1.85 g, 5.23 mmol) was added and the reaction mixture was left to stir at room temperature for 2 h. Water was added, the separated THF phase was collected and the aqueous phase was extracted with 3 portions of DCM. The THF and DCM portions were pooled, extracted with brine, dried over MgSO4 and evaporated. The residue was purified by column chromatography (SiO_2, 2/3 AcOEt/hexane) to give 0.50 g (1.25 mmol, 48%) of the title compound.

MS: m/e=400: M^+, 217 (100%): M^+- CF (CH_3)-PO_3Et_2, 57: tBu^+

NMR: ($CDCl_3$)

δ = 7.95 (t, J = 1.6 Hz, 2H) and 7.67 (t, 1H): arom. H

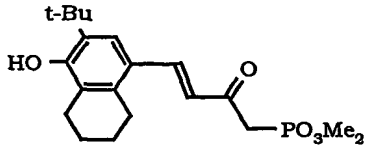
4.32-4.20 (m, 4H): P-O-$C\underline{H}_2$-CH_3

1.95 (dd, J = 24.1 and 15.3 Hz, 3H): -CF($C\underline{H}_3$)-P

1.36 (s, 18H): t-$C_4\underline{H}_9$

1.36 and 1.35 (two t, 6H): P-O-CH_2-$C\underline{H}_3$

Example 33: Dimethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-2-oxo-3-buten-1-yl phosphonate



A mixture of 3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaththaldehyde (5.09 g, 21.6 mmol), ethyl hydrogen malonate (8 g, 60.5 mmol), pyridine (8 ml, 99 mmol) and piperidine (0.43 ml, 4.3 mmol) was heated at 110°C for 7 h. To the cooled mixture were added water (50 ml) and a few drops of 10% HCl to bring the pH to ca 5 then the mixture was extracted with chloroform (threee 150 ml portions). The separated organic phase was added to 100 ml of a sodium hydroxide solution (pH = 9) and the resulting mixture was heated for 30 min. The chloroform phase was separated, the aqueous phase further extracted with fresh chloroform, the combined chloroform phases were dried, evaporated to dryness. The residue was purified by trituration in 40-60 petroleum ether to give 4 g (9.9 mmol, 46 %) of ethyl 3-[3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl]-acrylate.

Under nitrogen atmosphere dimethyl methylphosphonate (1.8 ml, 16.6 mmol) was added at –78°C to a solution of n-butyllithium (16 ml of a 1.6 M solution in hexane, 40 mmol) in 25 ml

anhydrous THF. The reaction mixture was stirred at -70° for 30 min to allow for complete formation of the lithium anion (slight turbidity). A solution of ethyl 3-[3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl]-acrylate (2.5 g, 8.3 mmol) in 10 ml dry THF was added. The resulting mixture was left to stir at room temperature (25°C) for 3 h. Hydrolysis was carried out by adding 10 ml of a saturated NH4Cl solution and the product was extracted into chloroform. After drying over $MgSO_4$, chloroform was evaporated and the residue was purified by column chromatography (SiO2, AcOEt/hexane 7/3) to give 0.89 g (2.34 mmol, 23%) of the title compound.

MS: m/e = 380: M^+, 362: $M^+ - H_2O$, 252: $M^+ - H_2O - HPO_3Me_2$, 57 (100%): tBu^+

NMR : ($CDCl_3$)

δ = 7.98 (d, J = 16Hz, 1H): Ph-C<u>H</u>=CH

7.48 (s, 1H): arom. H

6.68 (d, J = 16Hz, 1H): Ph-CH=C<u>H</u>

ca 5.3 (1H): OH

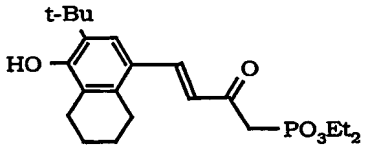
3.82 (d, J = 11 Hz, 6H): P-O-C<u>H</u>$_3$

3.35 (d, J = 22Hz, 2H): C<u>H</u>$_2$-P

2.86 (t, 2H), 2.59 (t, 2H), 1.89-1.82 (m, 2H) and 1.83-1.77 (m, 2H): C_4<u>H</u>$_8$

1.44 (s, 9H): t-C_4<u>H</u>$_9$

Example 34: Diethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-2-oxo-3-buten-1-yl phosphonate



Under nitrogen atmosphere diethyl methylphosphonate (3.8 g, 25 mmol) was added at –78°C to a solution of n-butyllithium (25 ml of a 1.6 M solution in hexane, 40 mmol) in 25 ml anhydrous THF. The reaction mixture was stirred at -70° for 30 min to allow for complete formation of the lithium anion (slight turbidity). A solution of ethyl 3-[3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl]-acrylate (2.0 g, 8.0 mmol) in 10 ml dry THF was added. The resulting mixture was left to stir at room temperature (25°C) for 3 h. Hydrolysis was carried out by adding 10 ml of a saturated NH4Cl solution and the product was extracted into chloroform. After drying over $MgSO_4$, chloroform was evaporated and the residue was purified by column

chromatography (SiO2, AcOEt/hexane 7/3) to give 0.77 g (2.34 mmol, 24%) of the title compound.

MS: m/e = 408: M^+, 390: $M^+ - H_2O$, 252: $M^+ - H_2O - HPO_3Et_2$, 57 (100%): tBu^+

NMR: ($CDCl_3$)

δ = 7.96 (d, J = 16Hz, 1H): Ph-C<u>H</u>=CH

7.46 (s, 1H): arom. H

6.70 (d, J = 16Hz, 1H): Ph-CH=C<u>H</u>

ca 5.3 (1H): OH

4.22-4.12 (m, 4H): P-O-C<u>H</u>$_2$-CH_3

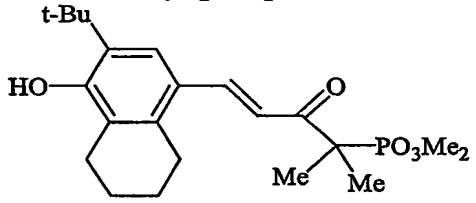
3.32 (d, J = 22Hz, 2H): C<u>H</u>$_2$-P

2.86 (t, 2H), 2.57 (t, 2H), 1.89-1.82 (m, 2H) and 1.83-1.76 (m, 2H): C_4<u>H</u>$_8$-

1.41 (s, 9H): t-C_4<u>H</u>$_9$

1.34 (t, J = 7Hz, 6H): P-O-CH_2-C<u>H</u>$_3$

Example 35: Dimethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate



To 30 ml dry THF kept at 0°C were added sequentially $TiCl_4$ (3.5 g, 18.0 mmol), 3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthaldehyde (1.5 g, 6.6 mmol), dimethyl 1,1-dimethyl-2-oxopropylphosphonate (1.6 g, 8.6 mmol), N-methyl morpholine (2.6 g, 26.4 mmol) then the reaction mixture was stirred for 45 min at room temperature. Work up was carried out by adding 50 ml of iced-water, extracting the resulting mixture with three portions of 100 ml dichloromethane, washing the organic phase with brine and drying over magnesium sulfate. Evaporation of the solvent gave a residue that was purified by trituration in petroleum ether. An amount of 1.7 g (4.16 mmol, 63 % yield) of the title compound was obtained.

MS: m/e = 408: M^+, 298: $M^+ - HPO_3Me_2$, 257: $M^+ - CMe_2(PO_3Me_2)$, 57 (100%): tBu^+

NMR: ($CDCl_3$)

δ = 8.15 (d, J = 18Hz, 1H): Ph-C<u>H</u>=CH

7.50 (s, 1H): arom. H

7.18 (d, J = 18Hz, 1H): Ph-CH=C<u>H</u>

ca 5.3 (1H): OH

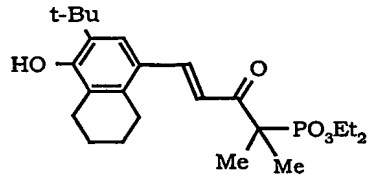
3.81 (d, J = 11 Hz, 6H): P-O-C$\underline{H}_3$

2.86, 2.59, 1.89-1.82, 1.83-1.76 and 1.48-1.38 (total 8H): $C_4\underline{H}_8$-

1.52 (d, J = 11 Hz, 6H): -C(C$\underline{H}_3$)$_2$-P

1.44 (s, 9H): t-$C_4\underline{H}_9$

Example 36: Diethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate



To 30 ml dry THF kept at 0°C were added sequentially $TiCl_4$ (2 ml, 18.0 mmol), 3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthaldehyde (1.5 g, 6.5 mmol), diethyl 1,1-dimethyl-2-oxopropylphosphonate (1.8 g, 8.0 mmol), N-methyl morpholine (2.5 ml, 26.4 mmol) then the reaction mixture was stirred for 45 min at room temperature. Work up was carried out by adding 50 ml of iced-water, extracting the resulting mixture with three portions of 100 ml dichloromethane, washing the organic phase with brine and drying over magnesium sulfate. Evaporation of the solvent gave a residue that was purified by column chromatography (SiO2, AcOEt/hexane 7/3). An amount of 2.21 g (4.16 mmol, 78 % yield) of the title compound was obtained.

MS: m/e = 436: M^+, 257: M^+ - $C(Me_2)PO_3Et_2$, 57 (100%): tBu^+

NMR: ($CDCl_3$)

δ = 7.99 (d, J = 16Hz, 1H): Ph-C$\underline{H}$=CH

7.50 (s, 1H): arom. H

7.22 (d, J = 16Hz, 1H): Ph-CH=C$\underline{H}$

ca 5.3 (1H): OH

4.18-4.12 (m, 4H): P-O-C$\underline{H}_2$-CH_3

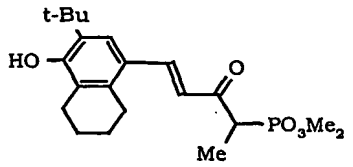
2.86 (t, 2H), 2.57 (t, 2H), 1.88-1.82 (m, 2H) and 1.82-1.76 (m, 2H): $C_4\underline{H}_8$-

1.51 (d, J = 16.7 Hz, 6H): -C(C$\underline{H}_3$)$_2$-P

1.43 (s, 9H): t-$C_4\underline{H}_9$

1.33 (t, J = 7Hz, 6H): P-O-CH_2-C$\underline{H}_3$

Example 37: Dimethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-1-methyl-2-oxo-3-buten-1-yl-phosphonate



To a suspension of sodium hydride (1.55 g of a 60% suspension in mineral oil, 64.66 mmol) in 60 ml THF was added a solution of 3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthaldehyde (6.0 g, 25.86 mmol) in 10 ml THF and the resulting mixture was stirred for 30 min at 0°C. 2-Methoxyethoxymethyl chloride (6.44 g, 51.72 mmol) was added dropwise and the resuting mixture was stirred for 4 h at room temperature. After hydrolysis by a saturated NH4Cl solution, the reaction mixture was partitioned between water and DCM. The dried organic phase was evaporated and the residue was purified by column chromatography (SiO2, DCM) to give 4.8 g of 3-tert-butyl-4-(2-methoxyethoxymethoxy)-5,6,7,8-tetrahydronaphthaldehyde (58%).

To a suspension of sodium hydride (0.90 g of a 60% suspension in mineral oil, 37.50 mmol) in 60 ml THF was added a solution of triethyl phosphonoacetate (4.03 g, 18 mmol) in 10 ml THF and the resulting mixture was stirred for 30 min at 0°C. 3-Tert-butyl-4-(2-methoxyethoxymethoxy)-5,6,7,8-tetrahydronaphthaldehyde (4.8 g, 15 mmol) was added dropwise and the resuting mixture was stirred for 2 h at room temperature. After hydrolysis by a saturated NH4Cl solution, the reaction mixture was partitioned between water and DCM. The dried organic phase was evaporated and the residue was purified by column chromatography (SiO2, 98/2 DCM/MeOH) to give 2.71 g of ethyl 3-[3-tert-butyl-4-(2-methoxyethoxymethoxy)-5,6,7,8-tetrahydronaphthyl] acrylate (46%).

n-Butyllithium (10.86 ml of a 1.6 M solution in hexane, 17.37 mmol) was added to 80 ml of THF cooled to –78°C, followed by dimethyl ethylphosphonate (2.4 g, 17.37 mmol). The resulting solution was stirred for 15 min at –78°C, then a solution of 2.71 g (6.95 mmol) of ethyl 3-[3-tert-butyl-4-(2-methoxyethoxymethoxy)-5,6,7,8-tetrahydronaphthyl] acrylate in 10 ml THF was added and the resulting reaction was left to stir at –78°C for 1 h. A saturated NH4Cl solution was added, the separated THF phase was collected and the aqueous phase was extracted with DCM. The THF and DCM portions were pooled, reextracted with brine, dried over MgSO4 and evaporated. The residue was purified by column chromatography (SiO2, 98/2 DCM/MeOH) to give 1.6 g (3.32 mmol, 47 %) of dimethyl 4-[3-tert-butyl-4-(2-methoxyethoxymethoxy)-5,6,7,8-tetrahydronaphthyl]-1-methyl-2-oxo-3-buten-1-yl-phosphonate .

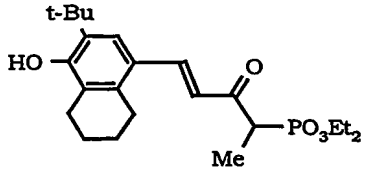
A mixture containing the latter compound (1.6 g, 3.32 mmol) and TFA (1.89 g, 16.6 mmol) in 50 ml DCM was stirred at room temperature for 1 h. A 10% sodium hydroxide solution was added until pH = 5-6, the aqueous solution extracted with DCM, dried and evaporated to dryness. Purification by column chromatography (SiO2, 98/2 DCM/MeOH gave 0.35 g (30%) of the title compound (mp=128-130°C after recrystallisation from DCM/Petroleum ether).

MS: m/e = 394: M^+, 376: $M^+ - H_2O$, 257: M^+- CHMe (PO_3Me_2), 57 (79%): tBu^+, 138 (100 %): HCHMe (PO_3Me_2) $^+$

NMR: ($CDCl_3$)

δ = 7.98 (d, J = 15.6Hz, 1H): Ph-C<u>H</u>=CH
7.49 (s, 1H): arom. H
6.79 (d, J = 15.6Hz, 1H): Ph-CH=C<u>H</u>
ca 5.3 (1H): OH
3.81 (2d, J = 11 Hz, 6H): P-O-C<u>H</u>$_3$
3.58-3.48 (2 quartets, 1H): C<u>H</u>(CH_3) -P
2.86, 2.59, 1.89-1.83 and 1.82-1.78 (total 8H): C_4<u>H_8</u>-
1.49 (2d, J = 7 Hz, 3H): -CH(C<u>H</u>$_3$) -P
1.43 (s, 9H): t-C_4H_9

Example 38: Diethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-1-methyl-2-oxo-3-buten-1-yl-phosphonate



Under nitrogen atmosphere diethyl ethylphosphonate (2.89 g, 17.38 mmol) was added at –78°C to a solution of n-butyllithium (10.9 ml of a 1.6 M solution in hexane, 17.38 mmol) in 75 ml anhydrous THF. The reaction mixture was stirred at -78° for 30 min to allow for complete formation of the lithium anion. A solution of ethyl 3-[3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl]-acrylate (2.1 g, 6.95 mmol) in 10 ml dry THF was added. The resulting mixture was left to stir at –78°C for 2 h, then at 25°C for 1h. Hydrolysis was carried out by adding 10 ml of a saturated NH_4Cl solution and the product was extracted into DCM. After drying over $MgSO_4$, DCM was evaporated and the residue was purified by column chromatography (SiO2, 98/2 DCM/MeOH) to give an oil that was further purified by

recrystallization from petroleum ether/DCM. An amount of 1.3 g (3.08 mmol, 44 %) of the title compound was obtained; mp=110-111°C.

MS: m/e = 422: M^+, 257: M^+ - CH(Me)PO_3Et_2, 57 (77%): tBu^+

NMR: ($CDCl_3$)

δ = 7.99 (d, J = 15.6Hz, 1H): Ph-C<u>H</u>=CH

7.49 (s, 1H): arom. H

6.82 (d, J = 15.6Hz, 1H): Ph-CH=C<u>H</u>

ca 5.3 (1H): OH

4.18-4.12 (m, 4H): P-O-C<u>H</u>$_2$-CH_3

3.53-3.43 (2 quartets, J= 7Hz, 1H): C<u>H</u>(CH_3) -P

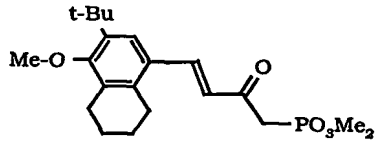
2.86 (t, 2H), 2.57 (t, 2H), 1.88-1.82 (m, 2H) and 1.82-1.76 (m, 2H): C_4<u>H</u>$_8$-

1.49 and 1.45 (2d, J = 7 Hz, 3H): -CH(C<u>H</u>$_3$) -P

1.43 (s, 9H): t-C_4<u>H</u>$_9$

1.33 (2t overlapped, J = 7Hz, 6H): P-O-CH_2-C<u>H</u>$_3$

Example 39: Dimethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-2-oxo-3-buten-1-yl phosphonate



A mixture of 3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthaldehyde (4.8 g, 18 mmol), ethyl hydrogen malonate (8 g, 61 mmol), pyridine (8 ml, 99 mmol) and piperidine (0.43 ml, 4.3 mmol) was heated at 110°C for 8 h. To the cooled mixture were added water (50 ml) and a few drops of 10% HCl to bring the pH to ca 5 then the mixture was extracted with chloroform (three 150 ml portions). The separated organic phase was added to 100 ml of a sodium hydroxide solution (pH = 9) and the resulting mixture was heated for 15 min. The chloroform phase was separated, the aqueous phase further extracted with fresh chloroform, the combined chloroform phases were dried, evaoparted to dryness. The resisue was purified by column chromatography (SiO2, AcOEt/hexane 5/95) to give 4 g (12.6 mmol, 70%) of ethyl 3-[3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl]-acrylate.

Under nitrogen atmosphere dimethyl methylphosphonate (2.5 g, 20 mmol) was added at -78°C to a solution of n-butyllithium (21 ml of a 1.6 M solution in hexane, 33 mmol) in 25 ml anhydrous THF. The reaction mixture was stirred at -70° for 30 min to allow for complete

formation of the lithium anion (slight turbidity). A solution of ethyl 3-[3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl]-acrylate (2.0 g, 6.6 mmol) in 10 ml dry THF was added. The resulting mixture was left to stir at room temperature (25°C) for 18 h. Hydrolysis was carried out by adding 10 ml of a 10% HCl solution and the product was extracted into chloroform. After drying over $MgSO_4$, chloroform was evaporated and the residue was purified by column chromatography (SiO2, AcOEt/hexane 8/2) to give 0.51 g (1.29 mmol, 20%) of the title compound.

MS: m/e = 394: M^+, 376: $M^+ - H_2O$, 266: $M^+ - H_2O - HPO_3Me_2$, 57 (100%): tBu^+

NMR: ($CDCl_3$)

δ = 8.01 (d, J = 16Hz, 1H): Ph-C<u>H</u>=CH

7.50 (s, 1H): arom. H

6.73 (d, J = 16Hz, 1H): Ph-CH=C<u>H</u>

3.86 (d, J = 11 Hz, 6H): P-O-C<u>H</u>$_3$

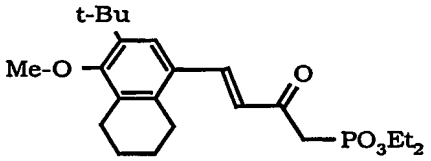
3.84 (s, 3H): arom. O-C<u>H</u>$_3$

3.39 (d, J = 22Hz, 2H): C<u>H</u>$_2$-P

2.92 (t, 2H), 2.81 (t, 2H), 1.91-1.86 (m, 2H) and 1.80-1.76 (m, 2H): C$_4$<u>H</u>$_8$-

1.44 (s, 9H): t-C$_4$<u>H</u>$_9$

Example 40: Diethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-2-oxo-3-buten-1-yl phosphonate



Under nitrogen atmosphere diethyl methylphosphonate (2.8 g, 18 mmol) was added at –78°C to a solution of n-butyllithium (19 ml of a 1.6 M solution in hexane, 30 mmol) in 25 ml anhydrous THF. The reaction mixture was stirred at -70° for 30 min to allow for complete formation of the lithium anion. A solution of ethyl 3-[3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl]-acrylate (1.9 g, 6.0 mmol) in 10 ml dry THF was added. The resulting mixture was left to stir at room temperature (25°C) for 4 h. Hydrolysis was carried out by adding 10 ml of a 10% HCl solution and the product was extracted into chloroform. After drying over $MgSO_4$, chloroform was evaporated and the residue was purified by column chromatography (SiO2, AcOEt/hexane 8/2) to give 0.79 g (1.87 mmol, 31%) of the title compound.

MS: m/e = 423: $M^+ + 1$, 404: $M^+ - H_2O$, 266: $M^+ - H_2O - HPO_3Et_2$, 57 (100%): tBu^+

NMR: ($CDCl_3$)

δ = 7.96 (d, J = 16Hz, 1H): Ph-C<u>H</u>=CH

7.45 (s, 1H): arom. H

6.71 (d, J = 16Hz, 1H): Ph-CH=C<u>H</u>

4.22-4.12 (m, 4H): P-O-C<u>H</u>$_2$-CH_3

3.79 (s, 3H): arom. O-C<u>H</u>$_3$

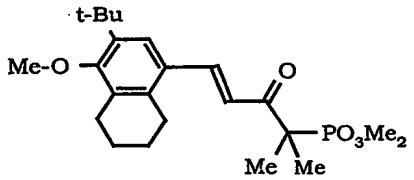
3.33 (d, J = 22Hz, 2H): C<u>H</u>$_2$-P

2.87 (t, 2H), 2.77 (t, 2H), 1.85-1.81 (m, 2H) and 1.74-1.71 (m, 2H): C_4<u>H</u>$_8$-

1.39 (s, 9H): t-C_4<u>H</u>$_9$

1.33 (t, J = 7Hz, 6H): P-O-CH_2-C<u>H</u>$_3$

Example 41: Dimethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate



Methyl iodide (5.6 ml, 0.09 mol) was added dropwise to a mixture of 3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthaldehyde (7.0 g, 0.031 mol), potassium carbonate (8 g, 0.06 mol), tetra-n-butylammonium bromide (0.8 g, 0.002 mol) dissolved in 10 ml of 2-butanone and the resulting mixture was refluxed for 3 h. The cooled mixture was filtered, the filtrate was concentrated under vacuum and partitioned between dichloromethane and water. Evaporation of the dried organic phase gave 7.3 g (0.030 mmol, 95% crude) of 3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthaldehyde.

To 30 ml dry THF kept at 0°C were added sequentially $TiCl_4$ (1.2 ml, 10.5 mmol), 3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthaldehyde (1.0 g, 4.1 mmol), dimethyl 1,1-dimethyl-2-oxopropylphosphonate (1.02 g, 5.3 mmol), N-methyl morpholine (2 ml, 16.4 mmol) then the reaction mixture was stirred for 2 h at room temperature. Work up was carried out by adding 50 ml of iced-water, extracting the resulting mixture with three portions of 100 ml dichloromethane, washing the organic phase with brine and drying over magnesium sulfate. Evaporation of the solvent gave a residue that was purified by trituration in petroleum ether. An amount of 0.52 g (1.23 mmol, 30 % yield) of the title compound was obtained.

MS: m/e =422: M^+, 312 (100%): M^+ -HPO_3Me_2, 271: M^+-$CMe_2(PO_3Me_2)$, 57: tBu^+

NMR: ($CDCl_3$)

δ = 8.04 (d, J = 15.4Hz, 1H): Ph-C<u>H</u>=CH

7.53 (s, 1H): arom. H

7.24 (d, J = 15.4Hz, 1H): Ph-CH=C<u>H</u>

3.84 (d, J = 11 Hz, 6H): P-O-C<u>H</u>$_3$

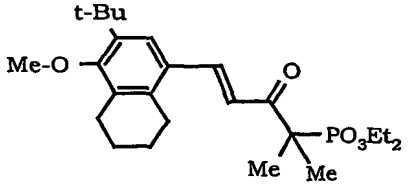
3.83 (s, 3H): arom. O-C<u>H</u>$_3$

2.90 (t, 2H), 2.80 (t, 2H), 1.90-1.83 (m, 2H) and 1.79-1.75 (m, 2H): C_4<u>H</u>$_8$-

1.56 (d, J = 16.7 Hz, 6H): -C(C<u>H</u>$_3$)$_2$-P

1.46 (s, 9H): t-C_4<u>H</u>$_9$

Example 42: Diethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate



The method described for the preceding example was followed, using the reactants in the following amounts: THF (50 ml), $TiCl_4$ (1.2 ml, 10.5 mmol), 3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthaldehyde (1.0 g, 4.1 mmol), diethyl 1,1-dimethyl-2-oxopropyl phosphonate (1.4 g, 5.3 mmol), N-methyl morpholine (2 ml, 16.4 mmol). An amount of 1.26 g (2.8 mmol, 68 % yield) of the title compound was obtained.

MS: m/e =450: M^+, 312 (100%): M^+ -HPO_3Et_2, 271: M^+-$CMe_2(PO_3Et_2)$, 57: tBu^+

NMR: ($CDCl_3$)

δ = 8.03 (d, J = 15.5Hz, 1H): Ph-C<u>H</u>=CH

7.53 (s, 1H): arom. H

7.23 (d, J = 15.5Hz, 1H): Ph-CH=C<u>H</u>

4.22-4.16 (quintet, 4H): P-O-C<u>H</u>$_2$-CH$_3$

3.83 (s, 3H): arom. O-C<u>H</u>$_3$

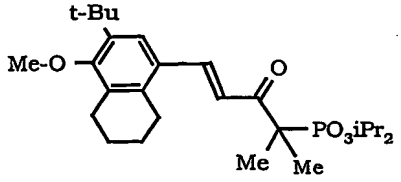
2.91 (t, 2H), 2.80 (t, 2H), 1.89-1.84 (m, 2H) and 1.79-1.75 (m, 2H): C_4<u>H</u>$_8$-

1.55 (d, J = 16.7 Hz, 6H): -C(C<u>H</u>$_3$)$_2$-P

1.45 (s, 9H): t-C_4<u>H</u>$_9$

1.37 (t, J = 7Hz, 6H): P-O-CH$_2$-C<u>H</u>$_3$

Example 43: Diisopropyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate



The method described for the preceding example was followed, using the reactants in the following amounts: THF (30 ml), $TiCl_4$ (1.4 ml, 12.2 mmol), 3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthaldehyde (1.0 g, 4.1 mmol), diisopropyl 1,1-dimethyl-2-oxopropyl phosphonate (1.3 g, 5.3 mmol), N-methyl morpholine (1.8 ml, 16.3 mmol). An amount of 0.93 g (1.95 mmol, 48 % yield) of the title compound was obtained.

MS: m/e =478: M^+, 312 (100%): M^+ -HPO_3iPr_2, 271: M^+-$CMe_2(PO_3iPr_2)$, 57: tBu^+

NMR: ($CDCl_3$)

δ = 7.96 (d, J = 15.5Hz, 1H): Ph-C<u>H</u>=CH

7.48 (s, 1H): arom. H

7.27 (d, J = 15.5Hz, 1H): Ph-CH=C<u>H</u>

4.74 (m, 4H): P-O-C<u>H</u>-$(CH_3)_2$

3.78 (s, 3H): arom. O-C<u>H</u>$_3$

2.86 (t, 2H), 2.76 (t, 2H), 1.84-1.79 (m, 2H) and 1.75-1.70 (m, 2H): C_4<u>H</u>$_8$-

1.47 (d, J = 16.7 Hz, 6H): -C(C<u>H</u>$_3)_2$-P

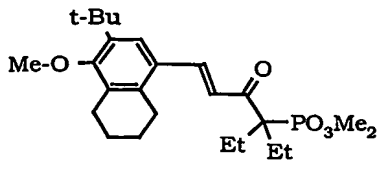
1.41 (s, 9H): t-C_4<u>H</u>$_9$

1.32 and 1.31 (2 d, 7Hz, 6H each): P-O-CH-(C<u>H</u>$_3)_2$

1.47 (s, 18H): t-C_4<u>H</u>$_9$

1.37 and 1.36 (2t, J = 7Hz, 6H): P-O-CH_2-C<u>H</u>$_3$

Example 44: Dimethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1,1-diethyl-2-oxo-3-buten-1-yl-phosphonate



The method described for the preceding example was followed, using the reactants in the following amounts: THF (20 ml), $TiCl_4$ (1.45 ml, 13.2 mmol), 3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthaldehyde (0.47 mmol,1.83 mmol), dimethyl 1,1-diethyl-2-oxopropyl

phosphonate (0.59 g, 2.36 mmol), N-methyl morpholine (0.80 ml 7.26 mmol). An amount of 0.25 g (0.56 mmol, 30 % yield) of the title compound was obtained.

MS: m/e =450: M^+, 271: M^+-$CEt_2(PO_3Me_2)$, 57 (100%): tBu^+

NMR: ($CDCl_3$)

δ = 7.98 (d, J = 15.4Hz, 1H): Ph-C<u>H</u>=CH

7.48 (s, 1H): arom. H

7.20 (d, J = 15.4Hz, 1H): Ph-CH=C<u>H</u>

3.80 (d, J= 11Hz, 6H): P-O-C<u>H</u>$_3$

3.79 (s, 3H): arom. O-C<u>H</u>$_3$

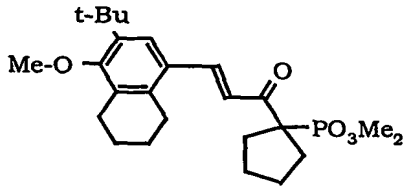
2.88 (t, 2H), 2.78 (t, 2H), 1.85-1.80 (m, 2H) and 1.75-1.70 (m, 2H): C_4<u>H</u>$_8$-

2.11-2.00 (m,4H): -C(C<u>H</u>$_2$-CH_3)$_2$-P

1.42 (s, 9H): t-C_4<u>H</u>$_9$

0.98 (t, J = 7.5 Hz, 6H): -C(CH_2-C<u>H</u>$_3$)$_2$-P

Example 45: Dimethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1,1-cyclopentyliden-2-oxo-3-buten-1-yl-phosphonate



The method described for the preceding example SR-158806 was followed, using the reactants in the following amounts: THF (20 ml), $TiCl_4$ (1.45 ml, 13.2 mmol), 3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthaldehyde (0.47 g, 1.83 mmol), dimethyl 1,1-cyclopentyliden-2-oxopropyl phosphonate (0.59 g 2.36 mmol), N-methyl morpholine 0.80 ml, 7.26 mmol). An amount of 0.31 g (0.69 mmmol, 38 % yield) of the title compound was obtained.

MS: m/e =448: M^+, 271: M^+-c-C_5H_8 (PO_3Me_2), 57 (100%): tBu^+

NMR: ($CDCl_3$)

δ = 8.00 (d, J = 15.4Hz, 1H): Ph-C<u>H</u>=CH

7.48 (s, 1H): arom. H

7.12 (d, J = 15.4Hz, 1H): Ph-CH=C<u>H</u>

3.80 (d, J= 10.3Hz, 6H): P-O-C<u>H</u>$_3$

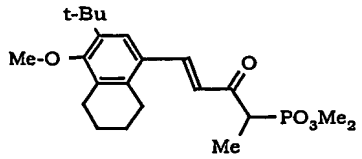
3.79 (s, 3H): arom. O-C<u>H</u>$_3$

2.88 (t, 2H), 2.78 (t, 2H), 1.85-1.78 (m, 2H) and 1.77-1.70 (m, 2H) (total 8H): $C_4\underline{H}_8$-

2.50-2.44 (m,2H), 2.25-2.15 (m,2H), 1.77-1.70 (m,2H),1.60-1.55 (m,2H) (total 8 H):-c-$C_5\underline{H}_8$-P

1.41 (s, 9H): t-$C_4\underline{H}_9$

Example 46: Dimethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1-methyl-2-oxo-3-buten-1-yl-phosphonate



Under nitrogen atmosphere dimethyl ethylphosphonate (4.6 g, 29 mmol) was added at –78°C to a solution of n-butyllithium (30 ml of a 1.6 M solution in hexane, 48 mmol) in 25 ml anhydrous THF. The reaction mixture was stirred at -70° for 30 min to allow for complete formation of the lithium anion. A solution of ethyl 3-[3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl]-acrylate (3.0 g, 9.5 mmol) in 10 ml dry THF was added. The resulting mixture was left to stir at room temperature (25°C) for 4 h. Hydrolysis was carried out by adding 10 ml of a saturated NH4Cl solution and the product was extracted into chloroform. After drying over $MgSO_4$, chloroform was evaporated and the residue was purified by column chromatography (SiO2, AcOEt/hexane 8/2) to give 0.98 g (2.4 mmol, 25%) of the title compound.

MS: m/e =408: M^+, 271: M^+-CHMe (PO_3Me_2), 138 (100%): HCHMe (PO_3Me_2), 57: tBu^+

NMR: ($CDCl_3$)

δ = 7.98 (d, J = 15.6Hz, 1H): Ph-C$\underline{H}$=CH

7.47(s, 1H): arom. H

6.81 (d, J = 15.6Hz, 1H): Ph-CH=C$\underline{H}$

3.80 and 3.79 (2d, J= 11Hz, 6H): P-O-C$\underline{H}_3$

3.79 (s, 3H): arom. O-C$\underline{H}_3$

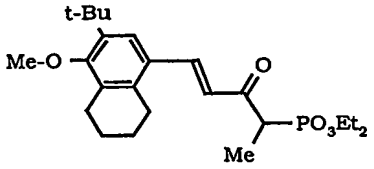
3.56 and 3.50 (2 quartets, J=7 Hz, 1H): C$\underline{H}$(CH_3)-P

2.87 (t, 2H), 2.76 (t, 2H), 1.85-1.80 (m, 2H) and 1.75-1.70 (m, 2H): $C_4\underline{H}_8$-

1.49 (2d, J = 7 Hz, H): -CH(C$\underline{H}_3$) -P

1.40 (s, 9H): t-$C_4\underline{H}_9$

Example 47: Diethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1-methyl-2-oxo-3-buten-1-yl-phosphonate



Under nitrogen atmosphere diethyl ethylphosphonate (2.63 g, 15.8 mmol) was added at -78°C to a solution of n-butyllithium (9.9 ml of a 1.6 M solution in hexane, 15.8 mmol) in 25 ml anhydrous THF. The reaction mixture was stirred at -78° for 30 min to allow for complete formation of the lithium anion. A solution of ethyl 3-[3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl]-acrylate (2.0 g, 6.3 mmol) in 10 ml dry THF was added. The resulting mixture was left to stir –78°C for 1 h. Hydrolysis was carried out by adding 10 ml of a saturated ammonium chloride solution and the product was extracted into dichloromethane (DCM). After drying over $MgSO_4$, DCM was evaporated and the residue was purified by column chromatography (SiO2, DCM/MeOH 98/2) to give 2.2 g (4.3 mmol, 82 %) of the title compound.

MS: m/e =436: M^+, 271: M^+-CHMe(PO_3Et_2), 57: tBu^+

NMR: ($CDCl_3$)

δ = 7.97 (d, J = 15.5Hz, 1H): Ph-C<u>H</u>=CH

7.48 (s, 1H): arom. H

6.84 (d, J = 15.5Hz, 1H): Ph-CH=C<u>H</u>

4.20-4.12 (m, 4H): P-O-C<u>H</u>$_2$-CH_3

3.79 (s, 3H): arom. O-C<u>H</u>$_3$

3.51 and 3.46 (2 quartets, J= 7Hz, 1H): -C<u>H</u>(CH_3)-P

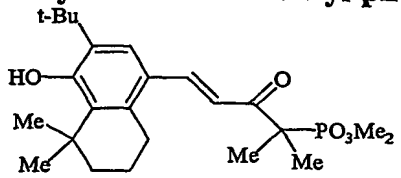
2.98 (t, 2H), 2.78 (t, 2H), 1.86-1.82 (m, 2H) and 1.76-1.70 (m, 2H): C_4<u>H</u>$_8$-

1.49 and 1.46 (2d, J = 7 Hz, 3H): -CH(C<u>H</u>$_3$)-P

1.40 (s, 9H): t-C_4<u>H</u>$_9$

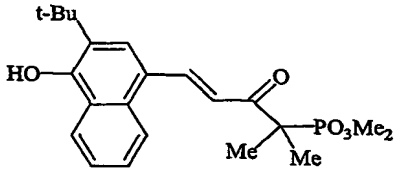
ca 1.37 (2 overlapped t, J = 7Hz, 6H): P-O-CH_2-C<u>H</u>$_3$

Example 48: Dimethyl 4-(3-tert-butyl-5,5-dimethyl-4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate



To 5 ml dry THF kept at 0°C were added sequentially $TiCl_4$ (87 mg, 0.46 mmol), 5,5-dimethyl-3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthaldehyde (50 mg, 0.192 mmol), dimethyl 1,1-dimethyl-2-oxopropylphosphonate (45 mg, 0.23 mmol), N-methyl morpholine (93 mg, 0.92 mmol) then the reaction mixture was stirred for 45 min at room temperature. Work up was carried out by adding iced-water, extracting the resulting mixture with dichloromethane, washing the organic phase with brine and drying over magnesium sulfate. Evaporation of the solvent gave a residue that was purified by column chromatography (SiO_2, 8/2 AcOEt/Hexane). An amount of 15 mg (0.034 mmol, 18 % yield) of the title compound was obtained.

Example 49: Dimethyl 4-(3-tert-butyl-4-hydroxy-1-naphthyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate



To 30 ml dry THF kept at 0°C were added sequentially $TiCl_4$ (2 ml, 2.9 g, 15.5 mmol), 3-tert-butyl-4-hydroxynaphthaldehyde (1.5 g, 6.6 mmol), dimethyl 1,1-dimethyl-2-oxopropylphosphonate (1.6 g, 7.83 mmol), N-methyl morpholine (2.5 ml, 3.12 g, 30.9 mmol) then the reaction mixture was stirred for 1 h at room temperature. Work up as previously described and purification by flash column chromatography (SiO_2, 7/3 AcOEt/hexane) gave 2.21 g (5.5 mmol, 82 % yield) of the title compound.

MS: m/e = 404: M^+, 253 (100%): M^+- $CMe_2(PO_3Me_2)$, 57 : tBu^+

NMR: ($CDCl_3$)

δ = 8.48 (d, J = 15 Hz, 1H): Ph-C<u>H</u>=CH

8.20, 8.13, 7.91, 7.53 (4m, 5H total): naphthyl H

7.39 (d, J = 15 Hz, 1H): Ph-CH=C<u>H</u>

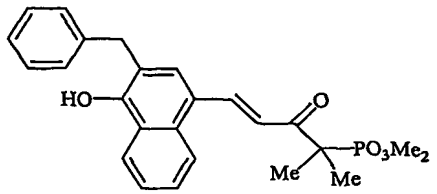
6.30 (broad s, 1H): OH

3.80 (d, J = 11Hz, 6H): P-O-C<u>H</u>$_3$

1.55 (d, J = 16.5 Hz, 6H): -C(C<u>H</u>$_3$)$_2$-P

1.54 (s, 9H): t-$C_4\underline{H}_9$

Example 50: Dimethyl 4-(3-benzyl-4-hydroxy-1-naphthyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate



To 20 ml dry THF kept at 0°C were added sequentially $TiCl_4$ (1.0 g, 5.3 mmol), 3-benzyl-4-hydroxynaphthaldehyde (0.6 g, 2.2 mmol), dimethyl 1,1-dimethyl-2-oxopropylphosphonate (0.54 g, 2.78 mmol), N-methyl morpholine (0.95 g, 9.3 mmol) then the reaction mixture was stirred for 1 h at room temperature. Work up as previously described and purification by flash column chromatography (SiO_2, 7/3 AcOEt/hexane) gave 0.91 g (2.1 mmol, 85 % yield) of the title compound.

MS: m/e = 438: M^+, 287 (100%): M^+- $CMe_2(PO_3Me_2)$, 91 (100%) : $C_7H_7^+$

NMR: ($CDCl_3$)

δ = 8.50 (d, J = 15.3 Hz, 1H) :Ph-C$\underline{H}$=CH

8.20, 8.22, 7.70, 7.55, 7.50: (5m, 5H total): naphthyl H

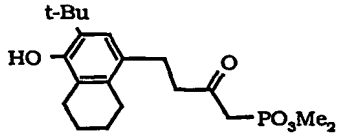
7.25 (m, 5H total): benzyl H

6.15 (broad s, 1H): OH

3.79 (d, J = 11Hz, 6H): P-O-C$\underline{H}_3$

1.55 (d, J = 16.5 Hz, 6H): -C(C$\underline{H}_3$)$_2$-P

Example 51: Dimethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-2-oxo-1-butyl-phosphonate



The title compound was obtained in 40% yield by reducing a solution of dimethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-2-oxo-3-buten-1-yl-phosphonate (0.20 g) over a suspension of Pd/C (0.15 g) in ethyl acetate.

MS: m/e=382: M^+, 325: M^+-t-Bu, 57 (100%): tBu^+

NMR ($CDCl_3$)

δ = 6.93 (s, 2H): arom. H

4.77 (s, 1H): OH

3.79 (d, J = 11.3Hz, 6H): P-O-C$\underline{H}_3$

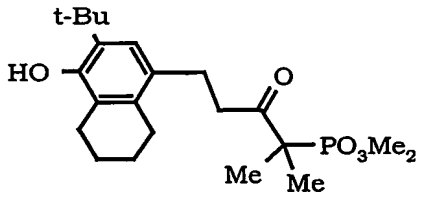
3.10 (d, J = 22.6Hz, 2H): C$\underline{H}_2$-P

2.88-2.79 (2m, 2H): Ph-C$\underline{H}_2$- CH_2 and Ph-CH_2-C$\underline{H}_2$

2.66 (t, 2H), 2.58 (t, 2H), 1.86-1.82 (m, 2H) and 1.81-1.76 (m, 2H): $C_4\underline{H}_8$-

1.41 (s, 9H): t-$C_4\underline{H}_9$

Example 52: Dimethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-1,1-dimethyl-2-oxo-1-butyl-phosphonate



A solution of dimethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate (0.50 g, 1.22 mmol) in 30 ml AcOEt was added to a suspension of Palladium over active charcoal (0.25 g) and the mixture was submitted to hydrogenation at room temperature in a Parr hydrogenation apparatus for 10 min. The reaction mixture was filtered over a pad of MgSO4, the filtrate was evaporated and the residue was purified by column chromatography (SiO2, 3/2 AcOEt/hexane). An amount of 0.4 g (1.07 mmol, 88%) of the title compound was obtained.

MS: m/e = 410: M^+, 353: M^+ – t-Bu, 300: M^+ - HPO_3Me_2, 57: tBu^+

NMR ($CDCl_3$)

δ = 6.93 (s, 1H): arom. H

4.80 (s, 1H): OH

3.76 (d, J = 11Hz, 6H): P-O-C$\underline{H}_3$

2.91 (distorted t, J = 7 Hz, 2H): Ph-C$\underline{H}_2$-CH_2

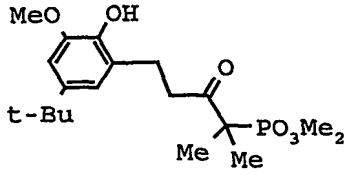
2.80 (distorted t, J = 7 Hz, 2H): Ph-CH_2-C$\underline{H}_2$

2.67 (t, 2H), 2.59 (t, 2H), 1.88-1.83 (m, 2H) and 1.80-1.75 (m, 2H): $C_4\underline{H}_8$-

1.43 (d, J = 17Hz, 6H): -C(C$\underline{H}_3$)$_2$-P

1.41 (s, 9H): t-$C_4\underline{H}_9$

Example 53: Dimethyl 4-(5-tert-butyl-2-hydroxy-3-methoxyphenyl)-1,1-dimethyl-2-oxo-1-butyl-phosphonate



The title compound was obtained in 80% yield by reducing a solution of dimethyl 4-(5-tert-butyl-2-hydroxy-3-methoxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate (0.20 g) over a suspension of Pd/C (0.15 g) in ethyl acetate.

MS: m/e = 386: M^+, 233: M^+- 2H - $CMe_2(PO_3Me_2)$, 57 : tBu^+

NMR: ($CDCl_3$)

δ = 6.77 and 6.75 (2d, 2H): arom. H

5.7 (s, 1H): OH

3.89 (s, 3H): arom. O-CH_3

3.75 (d, J = 11 Hz, 6H): P-O-$C\underline{H}_3$

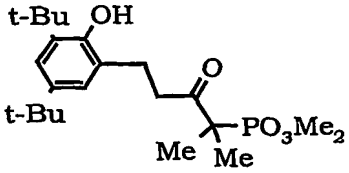
3.03 (t, J = 7 Hz, 2H): Ph-$C\underline{H}_2$-CH_2

2.89 (t, J = 7 Hz, 2H): Ph-CH_2-$C\underline{H}_2$

1.42 (d, J = 16.9Hz, 6H): -$C(C\underline{H}_3)_2$-P

1.29 (s, 9H): t-$C_4\underline{H}_9$

Example 54: Dimethyl 4-(3,5-di-tert-butyl-2-hydroxyphenyl)-1,1-dimethyl-2-oxo-1-butyl-phosphonate



The title compound was obtained in 40% yield by reducing a solution of dimethyl 4-(3,5-di-tert-butyl-2-hydroxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate (0.20 g) over a suspension of Pd/C (0.15 g) in ethyl acetate.

MS: m/e = 412: M^+, 259: M^+- 2H - $CMe_2(PO_3Me_2)$, 57: tBu^+

BIOLOGICAL RESULTS

Example 55: HMG-CoA Reductase Assay

The ability of compounds of Formula (I) to affect HMG-CoA levels was investigated in the HeLa cell line obtained from the American Type Culture Collection organization (ATCC).

A. Experimental Protocol

Quantification of HMGR levels by Immunoblotting

HeLa cells (ATCC) were seeded in 6 wells plates (8.10^5 cells per well) in DMEM containing 10% fetal calf serum (FCS) and grown for 1 day. Then, the medium was replaced by DMEM without FCS and the cells were further grown for 16 h. Products were tested at 1 and 10 μM final concentrations; they were added as 1000-fold concentrated stock solutions in 50% EtOH and 50% DMSO. After a 5 h incubation period, cells were washed in ice cold PBS and lysed in 200 μl/well of the following buffer: 20 mM Hepes pH 7.4, 50 mM NaCl, 10 mM EDTA, 10 mM EGTA, 2.2% DMSO, 1% Triton X-100 and the Complete Protease Inhibitor cocktail (Roche Diagnostics). Cells were kept for 15 min on ice; then, cell lysates were collected and spun at 14K rpm for 20 min. The supernatants were kept and protein concentrations were determined using the BioRad DC protein assay (BioRad). Samples were diluted in sample buffer containing 5% β-mercaptoethanol and loaded on 7.5% SDS-PAGE without prior boiling. HMG-CoA reductase levels were analysed by subsequent immunoblotting using mouse A9 mAbs (hybridoma cells CRL-1811; ATCC). Bound A9 antibodies were revealed by goat anti-mouse IgG peroxidase-coupled antibodies (Sigma) and SuperSignal West Dura Extended Duration Substrate (Pierce) followed by autoradiography.

B. Results

Compounds (I) were tested at two different concentrations: 1 and 10 μM. The relative potencies of Compounds (I) for decreasing HMG-CoA reductase were expressed as approximative % change of samples treated with 10 μM test compounds of Formula (I) over control samples. HMG-CoA reductase levels were estimated by comparing samples from treated cells with samples from non-treated cells. Estimation of the effect of the compounds was established as follows:

++++ is 100% decrease in HMGR levels at 10 and at 1 μM

+++ is 100% decrease in HMGR levels at 10 μM /50-99% at 1 μM

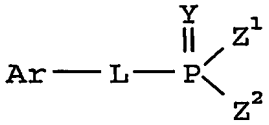
++ is 50-99% decrease in HMGR levels at 10 μM / 0-50% at 1 μM

+ is 10-49% decrease in HMGR levels at 10 μM / 0% at 1 μM

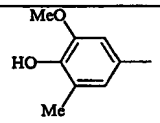
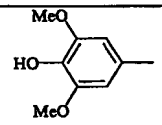
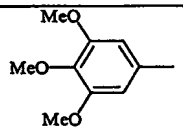
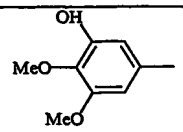
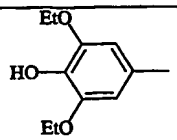
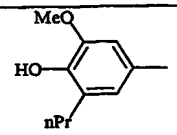
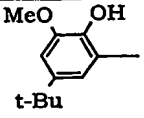
(+) is 1-10% decrease in HMGR levels at 10 μM / 0% at 1 μM.

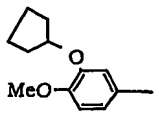
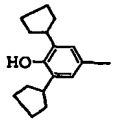
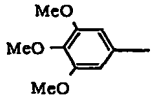
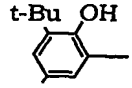
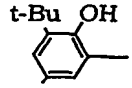
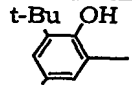
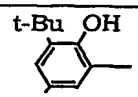
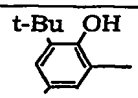
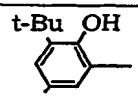
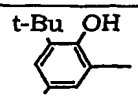
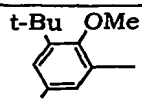
The results are summarized in TABLE 1.

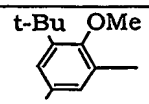
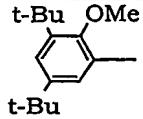
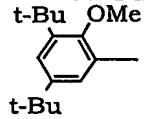
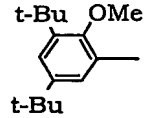
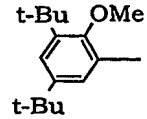
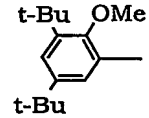
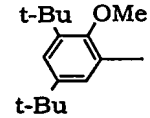
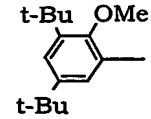
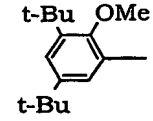
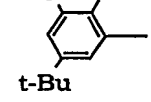
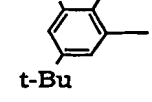
TABLE 1 - Reduction in the amount of HMG-CoA reductase by Compounds of Formula (I) wherein Y is O

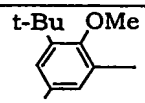
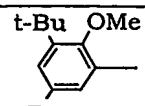
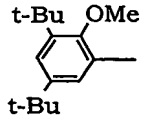
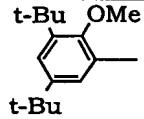
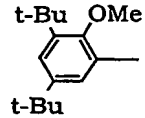
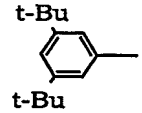
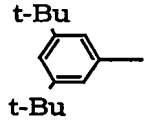
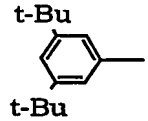
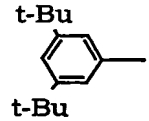
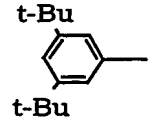
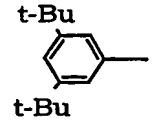


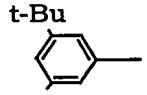
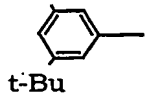
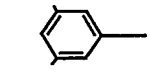
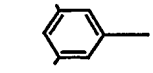
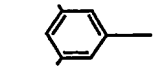
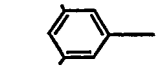
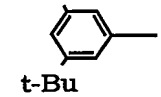
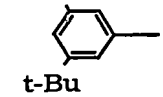
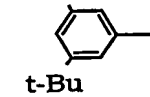
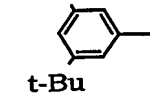
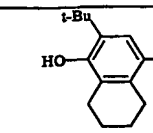
(I)

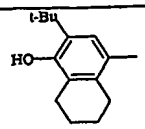
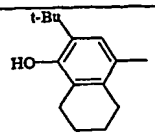
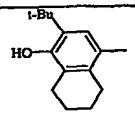
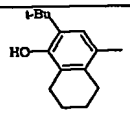
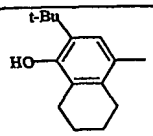
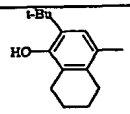
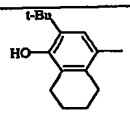
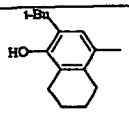
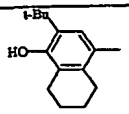
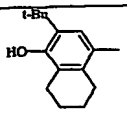
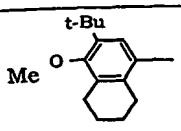
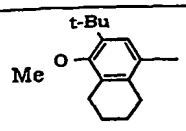
Cpd N°	Ar	L	Z^1, Z^2	Relative Potency
1		CH=CH-C(O)-C(Me)$_2$	OMe	(+)
2		CH=CH-C(O)-C(Me)$_2$	OMe	(+)
3		CH=CH-C(O)-C(Me)$_2$	OMe	+
4		CH=CH-C(O)-C(Me)$_2$	OMe	(+)
5		CH=CH-C(O)-C(Me)$_2$	OMe	(+)
6		CH=CH-C(O)-C(Me)$_2$	OMe	(+)
7		CH=CH-C(O)-C(Me)$_2$	OMe	(+)

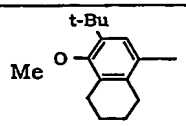
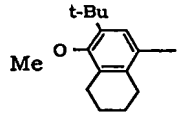
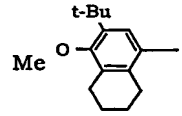
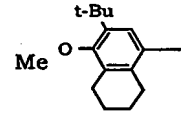
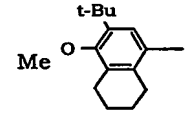
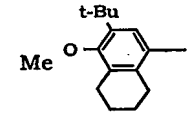
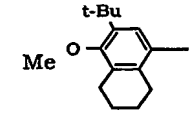
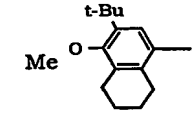
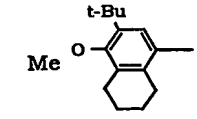
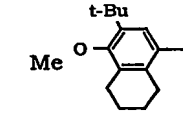
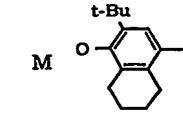
Cpd N°	Ar	L	Z^1, Z^2	Relative Potency
8		CH=CH-C(O)-C(Me)$_2$	OMe	(+)
9		CH=CH-C(O)-C(Me)$_2$	OMe	++
10		C(O)-C(Me)$_2$	OMe	< (+)
11		CH=CH-C(O)-C(Me)$_2$	OMe	+++(+)
12		CH=CH-C(O)-C(Me)$_2$	OEt	+++(+)
13		CH=CH-C(O)-C(Et)$_2$	OMe	++
14		CH=CH-C(O)-C(Et)$_2$	OEt	+++
15		CH=CH-C(O)-C(c-C_5H_8)	OMe	++
16		CH=CH-C(O)-C(c-C_5H_8)	OEt	++
17		CH=CH-C(O)-CF(Me)	OEt	++
18		CH=CH-C(O)-CH$_2$	OMe	++

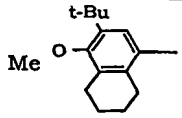
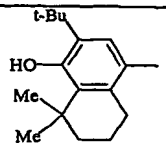
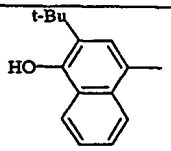
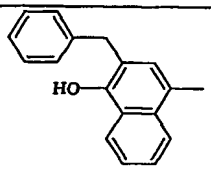
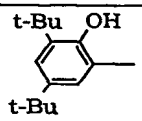
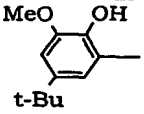
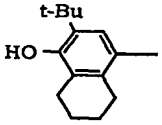
Cpd N°	Ar	L	Z^1, Z^2	Relative Potency
19		CH=CH-C(O)-CH_2	OEt	+
20		CH=CH-C(O)-$C(Me)_2$	OMe	++
21		CH=CH-C(O)-$C(Me)_2$	OEt	++
22		CH=CH-C(O)-$C(Me)_2$	OiPr	+
23		CH=CH-C(O)-CH(Me)	OMe	+
24		CH=CH-C(O)-CH(Me)	OEt	+
25		CH=CH-C(O)-CF(Me)	OMe	+
26		CH=CH-C(O)-CF(Me)	OEt	+
27		CH=CH-C(O)-CF_2	OMe	++
28		CH=CH-C(O)-CF_2	OEt	++
29		CH=CH-C(O)-$C(Et)_2$	OMe	+

Cpd N°	Ar	L	Z^1, Z^2	Relative Potency
30		CH=CH-C(O)-C(c-C_5H_8)	OMe	+
31		C(O)-CH(Me)	OEt	(+)
32		C(O)-$C(Me)_2$	OEt	+
33		C(O)-CF(Me)	OMe	+
34		C(O)-CF(Me)	OEt	+
35		CH=CH-C(O)-CH_2	OMe	(+)
36		CH=CH-C(O)-CH_2	OEt	(+)
37		CH=CH-C(O)-$C(Me)_2$	OMe	++
38		CH=CH-C(O)-$C(Me)_2$	OEt	++
39		CH=CH-C(O)-C(Me)(Et)	OMe	++
40		CH=CH-C(O)-$C(Et)_2$	OMe	+(+)

Cpd N°	Ar	L	Z^1, Z^2	Relative Potency
41		CH=CH-C(O)-C(c-C_5H_8)	OMe	++(+)
42		CH=CH-C(O)-CF_2	OMe	+
43		CH=CH-C(O)-CF_2	OEt	
44		C(O)-CH(Me)	OMe	(+)
45		C(O)-CH(Me)	OEt	(+)
46		C(O)-$C(Me)_2$	OMe	+
47		C(O)-$C(Me)_2$	OEt	+
48		C(O)-CF(Me)	OMe	+(+)
49		C(O)-CF(Me)	OEt	+(+)
50		C(O)-CF_2	OMe	(+)
51		CH=CH-C(O)-CH_2	OMe	++

Cpd N°	Ar	L	Z^1, Z^2	Relative Potency
52		CH=CH-C(O)-CH_2	OEt	++
53		CH=CH-C(O)-$C(Me)_2$	OMe	+++
54		CH=CH-C(O)-$C(Me)_2$	OEt	++
55		CH=CH-C(O)-CH(Me)	OMe	++
56		CH=CH-C(O)-CH(Me)	OEt	++
57		CH=CH-C(O)-CF(Me)	OMe	
58		CH=CH-C(O)-CF(Me)	OEt	++
59		CH=CH-C(O)-C(Me)(Et)	OMe	++
60		CH=CH-C(O)-$C(Et)_2$	OMe	++
61		CH=CH-C(O)-C(c-C_5H_8)	OMe	++
62		CH=CH-C(O)-CH_2	OMe	++
63		CH=CH-C(O)-CH_2	OEt	+++

Cpd N°	Ar	L	Z^1, Z^2	Relative Potency
64		CH=CH-C(O)-$C(Me)_2$	OMe	+++
65		CH=CH-C(O)-$C(Me)_2$	OEt	++(+)
66		CH=CH-C(O)-$C(Me)_2$	OiPr	++
67		CH=CH-C(O)-CH(Me)	OMe	++
68		CH=CH-C(O)-CH(Me)	OEt	++
69		CH=CH-C(O)-CF(Me)	OMe	
70		CH=CH-C(O)-CF(Me)	OEt	++
71		CH=CH-C(O)-C(Me)(Et)	OMe	+++
72		CH=CH-C(O)-$C(Et)_2$	OMe	++
73		CH=CH-C(O)-C(c-C_5H_8)	OMe	++
74		C(O)-CH(Me)	OEt	+

Cpd N°	Ar	L	Z^1, Z^2	Relative Potency
75		C(O)-C(F)(Me)	OEt	++
76		CH=CH-C(O)-C(Me)$_2$	OMe	+
77		CH=CH-C(O)-C(Me)$_2$	OMe	++
78		CH=CH-C(O)-C(Me)$_2$	OMe	++
79		CH_2-CH_2-C(O)-C(Me)$_2$	OMe	+
80		CH_2-CH_2-C(O)-C(Me)$_2$	OMe	< (+)
81		CH_2-CH_2-C(O)-C(Me)$_2$	OMe	(+)

Example 56: *In Vivo* Murine Bone Anabolic Activity Model

The bone anabolic activity of selected compounds of Formula (I) displaying potent HMG-CoA reducing activity was investigated in mice. This species has been used extensively to study the genetic, physiologic and pharmacologic regulation of bone metabolism and has been shown to be a relevant model.

A. Experimental Protocol

Male OF1 mice (Charles River, France), weighing ca 30g were divided into groups of 6 animals. Animals were maintained on a 12 h-12 h light cycle and were fed ad libitum with UAR

A03 (France) chow. The calcium and phosphorus contents of the food were respectively 0.8% and 0.6%. Food consumption and body weight were measured on a weekly basis.

Control group received standard chow and Treated groups received test compounds mixed with the diet, at the required concentration to the targeted dose level. Doses used varied from 12.5 mg/kg to 100 mg/kg. Active compounds showed activity around the minimal dose 12.5 mg/kg.

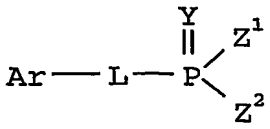
At the end of the treatment period (4 weeks) animals were sacrificed, blood was collected, serum was obtained and femurs and vertebra were dissected and frozen. Bone mineral content measurements were performed employing a bone scanner (XCT research series, Stratec, Germany). Measurements were made in the trabecular-rich distal metaphyseal region of the femurs or in the proximal head of the lumbar vertebras and the following bone parameters were measured: trabecular and cortical density in femurs and trabecular density in vertebrs. The analysis parameters were: peelmode 4, threshold 280 mg/cm^3, inner threshold 500 mg/cm^3 and peel 5%.

Briefly the XCT Bone Scanner is a fully automated measuring system based on the Peripheral Quantitative Computer Tomography (pQCT) technique for the determination of bone density. The pQCT technique is a highly sensitive method that allows the monitoring of bone loss and bone gain over time in a non-invasive manner. It has been validated for measuring bone parameters in mice treated with bone anabolic agents such as the hormone PTH and the antiresorptive bisphosphonic acids (see Feretti et al, 1996 and Gasser, 1995). It has been shown previously that the pQTC technique employed correlates with bone dry weight. For instance, results published by Rosenberg et al (Osteoporosis International, 5, 47-53 (1995)) indicate that bone dry weight, after complete mineralisation at 800°C, was highly correlated with bone mineral content (BMC) as measured by pQCT.

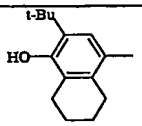
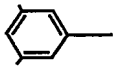
B. Results

Table 2 shows that two representative compounds of Formula (I) markedly increase bone formation: at 12.5mg/kg, Compounds **52** and **37** increased vertebra trabercular density by respectively 11 and 26 %; furthermore at 50 mg/kg Compound **37** increased the vertebra density by 57 %. The compounds of the present invention are thus useful in pharmaceutical formulations for the prevention and treatment of diseases where bone growth is necessary.

Table 2 - *In Vivo* effect of Compounds of Formula (I), wherein Y is O, on Mouse Bone



(I)

Cpd	Ar	L	Z^1, Z^2	Vertebra Trabecular Density (% control)
52		CH=CH-C(O)-CH_2	OEt	+11 @ 12.5 mg/kg
37	t-Bu  t-Bu	CH=CH-C(O)-$C(Me)_2$	OMe	+26 @ 12.5 mg/kg, ($p < 0.01$) +57 @ 50 mg/kg,($p < 0.001$)

Example 57: Tablet Formation

A tablet composition containing a compound of formula (I) is prepared by mixing and compressing in a tablet making machine the flowing ingredients: 200 mg compound of formula (I); 200 mg lactose; and 20 mg magnesium stearate.

REFERENCES

The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

Berge *et al.*, "*Pharmaceutical salts*," J. Pharm. Sci., 66:1-19, 1977.

Garnero *et al.*, "*Markers of bone turnover for the management of patients with bone metastasis from prostate cancer*," Br. J. Cancer, 82:858-64, 2000.

Ferretti *et al.*, Bone 18 (2): 97-102 (1996)

Gasser, Bone 17 (4), 145S- 154S

Mathey & Savignac, Tetrahedron 34:649-654, 1978.

Mundy *et al.*, "*Stimulation of bone formation in vitro and in rodents by statins*," Science, 286:1946-1949, 1999.

Roussis & Wiemer, J. Org. Chem., 54:627-631, 1989.